PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 March 2000 (08.03.00)	
International application No. PCT/CA99/00600	**Applicant's or agent's file reference** T8464029WO
International filing date (day/month/year) 30 June 1999 (30.06.99)	**Priority date** (day/month/year) 02 July 1998 (02.07.98)
Applicant PON, Richard, T. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 February 2000 (02.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

NASSIF, Omar, A.
Gowling Lafleur Henderson LLP
Suite 4900
Commerce Court West
Toronto, Ontario M5L 1J3
CANADA

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 22 August 2000 (22.08.00)	
Applicant's or agent's file reference T8464029WO	**IMPORTANT NOTIFICATION**
International application No. PCT/CA99/00600	**International filing date** (day/month/year) 30 June 1999 (30.06.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
NASSIF, Omar, A. Gowling, Strathy & Henderson Suite 4900 Commerce Court West Toronto, Ontario M5L 1J3 Canada		

Telephone No.: 416-862-5775
Facsimile No.: 416-862-7661
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
NASSIF, Omar, A. Gowling Lafleur Henderson LLP Suite 4900 Commerce Court West Toronto, Ontario M5L 1J3 Canada		

Telephone No.: 416-862-5775
Facsimile No.: 416-862-7661
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREA

RECEIVED

NOV 22 1999

GOWLING, STRATHY & HENDERSON
PATENT DEPARTMENT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GOWLING, STRATHY & HENDERSON
Attn. NASSIF, Omar A.
Suite 4900
Commerce Court West
Toronto, Ontario M5L 1J3
CANADA

Applicant's or agent's file reference T8464029WO	Date of mailing *(day/month/year)* 17/11/1999
International application No. PCT/CA 99/ 00600	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant UNIVERSITY TECHNOLOGIES INTERNATIONAL INC. et al.	International filing date *(day/month/year)* 30/06/1999

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk	John De Bruijn

ES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
T8464029WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00600	30/06/1999	02/07/1998

Applicant

UNIVERSITY TECHNOLOGIES INTERNATIONAL INC. et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   REUSABLE SOLID SUPPORT FOR OLIGONUCLEOTIDE SYNTHESIS

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [X] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PON R T ET AL: "Hydroquinone-O,O@?-Diacetic Acid As A More Labile Replacement For Succinic Acid Linkers in Solid-Phase Oligonucleotide Synthesis" TETRAHEDRON LETTERS, vol. 38, no. 19, 12 May 1997 (1997-05-12), page 3327-3330 XP004061417 ISSN: 0040-4039	1-187
X	the whole document, but especially the CPG derivatised nucleotide of scheme 2	1-6, 8-12,15, 42, 45-50, 53-58, 60-66, 94, 97-102, 105, 185-187

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1999	17/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040 Tx. 31 651 epo nl	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 23496 A (UNIV TECHNOLOGIES INT ;PON RICHARD T (CA); YU SHUYUAN (CA)) 3 July 1997 (1997-07-03)	1-187
X	the whole document	1-14,42, 45-66, 94, 97-105, 185-187
Y	WO 97 23497 A (UNIV TECHNOLOGIES INT ;PON RICHARD T (CA); YU SHUYUAN (CA)) 3 July 1997 (1997-07-03)	1-187
X	the whole document	1-6, 8-12,15, 42, 45-50, 53-58, 60-66, 94, 97-102, 105, 185-187
Y	US 5 624 711 A (SUNDBERG STEVEN A ET AL) 29 April 1997 (1997-04-29) the whole document	1-187
Y	PON R T ET AL: "Rapid Automated Derivatization of Solid-Phase Supports For Oligonucleotide Synthesis Using Uronium or Phosphonium Coupling Reagents" TETRAHEDRON LETTERS, vol. 38, no. 19, 12 May 1997 (1997-05-12), page 3331-3334 XP004061418 ISSN: 0040-4039 the whole document	1-187
Y	WO 92 06103 A (ICI PLC) 16 April 1992 (1992-04-16) the whole document	1-187
Y	WO 93 07883 A (ISIS PHARMACEUTICALS INC) 29 April 1993 (1993-04-29) the whole document	1-187

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INTERNATIONAL SEARCH REPORT

International Application No
CT/CA 99/00600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	JAMES I W: "Linkers for Solid Phase Organic Synthesis" TETRAHEDRON, vol. 55, no. 16, 16 April 1999 (1999-04-16), page 4855-4946 XP004161079 ISSN: 0040-4020 page 4859, compound a; page 4865, compound 4; the whole document	1-187

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
CT/CA 99/00600

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9723496 A	03-07-1997	AU 1027797 A	17-07-1997
		AU 1027897 A	17-07-1997
		CA 2241222 A	03-07-1997
		CA 2241331 A	03-07-1997
		WO 9723497 A	03-07-1997
		EP 0876390 A	11-11-1998
		EP 0877751 A	18-11-1998
WO 9723497 A	03-07-1997	AU 1027797 A	17-07-1997
		AU 1027897 A	17-07-1997
		CA 2241222 A	03-07-1997
		CA 2241331 A	03-07-1997
		WO 9723496 A	03-07-1997
		EP 0876390 A	11-11-1998
		EP 0877751 A	18-11-1998
US 5624711 A	29-04-1997	US 5919523 A	06-07-1999
WO 9206103 A	16-04-1992	AU 665174 B	21-12-1995
		AU 8650991 A	28-04-1992
		CA 2093356 A	05-04-1992
		EP 0552185 A	28-07-1993
		JP 6501692 T	24-02-1994
WO 9307883 A	29-04-1993	AU 2916292 A	21-05-1993
		CA 2122030 A,C	29-04-1993
		EP 0724447 A	07-08-1996
		JP 2823959 B	11-11-1998
		JP 6510791 T	01-12-1994
		US 5578718 A	26-11-1996
		US 5852182 A	22-12-1998

PATENT COOPERATION TREATY

PCT 04 OCT 2000

WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
T8464029WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00600	30/06/1999	02/07/1998
International Patent Classification (IPC) or national classification and IPC C07H21/00		
Applicant UNIVERSITY TECHNOLOGIES INTERNATIONAL INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/02/2000	02.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Authorized officer Korsner, S-E

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00600

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-41 as originally filed

Claims, No.:

1-187 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	to be settled in a later phase - see below
	No:	Claims	idem
Inventive step (IS)	Yes:	Claims	to be settled in a later phase - see below
	No:	Claims	idem
Industrial applicability (IA)	Yes:	Claims	1-187
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. Reasoned statement

The following documents will be referred to in this report:

D1 = Tetrahedron Letters; 1997, Vol. 38, pages 3327-3330
&
D2 = Tetrahedron Letters; 1997, Vol. 38, pages 3331-3334

1. Novelty (Article 33(2) PCT)

It is evident already from the background art review, e.g. page 4, that prior art linkers fall under the very broad drafting of Claims 1-15.
Such drafting is merely speculative and does not sufficiently define the matter for which protection is sought.
It is the Applicant's task to clearly define the linkers which are the result of his inventive activity and which are supported by a factual teaching in the Description.

It appears that the characteristic part of the invention is the T-portion, but such ideas are obviously disclosed in D1 and, in particular D2, including examples with QDA and succinyl linkers.

2. Inventive step (Article 33(3) PCT)

Once the general idea of alternative linkers to the solid support was made available in D1-D2, the skilled man would of course be able to suggest such uses also in connection with other linkers than those specifically exemplified in D2.

To what extent this could have been done has to be further settled in a later phase; the Applicant has chosen not to provide any further information (or restriction of the claims) during the international phase.

It appears from the many definitions of T that a non-unity problem may arise in case the Applicant restores novelty or inventive step in such a way that separate embodiments result.
At least one inventive feature (supposedly a T-portion characteristics) should be present throughout all the claims in order to meet the requirement for unity under Rule 13 PCT [other considerations may possibly apply in certain national phases].

VIII. Certain observations

Claims:

1.
The excessive number of claims should be reduced by using claim dependency. For instance, the nucleosides of Claim 53 could be added to Claim 1:
-> $[Nucleoside]_{0-1}$ - Z..... (because Claim 1 already refers to oligonucleotide synthesis) and Claims 53-104 may then be deleted.

Alternatively, Claim 53 could refer to "A linker arm as defined in a preceding claim which further contains a nucleoside linked to Z" (or a similar wording).

Claim 106 could refer to the preceding claims with the deletion of Claims 107-140 (which are repetitions of Claims 2-52).

Claims 145-178 could be deleted and a claim dependency introduced in Claim 144. Similar simplifications are possible also in the final claims.

[The above may be subject to certain national regulations, but should be made at least in a later European phase.]

2.
Claims 24-26 are identical with Claims 18-20.

Description:

3.
The "hereby incorporated by reference" (page 1 and later) is not normally acceptable under all national/regional regulations [e.g. in the European phase]; especially if the documents were not available to the public in time.

4.
The "preferably" on page 10, lines 7-9, is unclear because a carbon atom would anyway be expected to be present in an organic radical.

5.
The formula on page 12 must be incorrect; see the oxygen on the left hand side.
Moreover, there is no corresponding formula in the Claims.
See also the left-hand oxygen in the formula on page 13.

6.
The terms "Tentagel" and "Toyopearl" on page 33 seem to be registered trade marks and should, if so, be identified as such.

7.
The Description should be revised to correspond to any amended claims and irrelevant matter should be deleted.

8.
D1-D2 should be identified as background art under Rule 5.1(a)(ii) PCT.

- - - - -

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
T8464029WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00600	30/06/1999	02/07/1998
Applicant		
UNIVERSITY TECHNOLOGIES INTERNATIONAL INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

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[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

REUSABLE SOLID SUPPORT FOR OLIGONUCLEOTIDE SYNTHESIS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[ ] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[X] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PON R T ET AL: "Hydroquinone-O,O@?-Diacetic Acid As A More Labile Replacement For Succinic Acid Linkers in Solid-Phase Oligonucleotide Synthesis" TETRAHEDRON LETTERS, vol. 38, no. 19, 12 May 1997 (1997-05-12), page 3327-3330 XP004061417 ISSN: 0040-4039	1-187
X	the whole document, but especially the CPG derivatised nucleotide of scheme 2	1-6, 8-12,15, 42, 45-50, 53-58, 60-66, 94, 97-102, 105, 185-187

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1999	17/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scott, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	the whole document	1-14,42, 45-66, 94, 97-105, 185-187
Y	WO 97 23497 A (UNIV TECHNOLOGIES INT ;PON RICHARD T (CA); YU SHUYUAN (CA)) 3 July 1997 (1997-07-03)	1-187
X	the whole document	1-6, 8-12,15, 42, 45-50, 53-58, 60-66, 94, 97-102, 105, 185-187
Y	US 5 624 711 A (SUNDBERG STEVEN A ET AL) 29 April 1997 (1997-04-29) the whole document	1-187
Y	PON R T ET AL: "Rapid Automated Derivatization of Solid-Phase Supports For Oligonucleotide Synthesis Using Uronium or Phosphonium Coupling Reagents" TETRAHEDRON LETTERS, vol. 38, no. 19, 12 May 1997 (1997-05-12), page 3331-3334 XP004061418 ISSN: 0040-4039 the whole document	1-187
Y	WO 92 06103 A (ICI PLC) 16 April 1992 (1992-04-16) the whole document	1-187
Y	WO 93 07883 A (ISIS PHARMACEUTICALS INC) 29 April 1993 (1993-04-29) the whole document	1-187

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
T	JAMES I W: "Linkers for Solid Phase Organic Synthesis" TETRAHEDRON, vol. 55, no. 16, 16 April 1999 (1999-04-16), page 4855-4946 XP004161079 ISSN: 0040-4020 page 4859, compound a; page 4865, compound 4; the whole document	1-187

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00600

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PON, Richard, T. [CA/CA]; 108 Ranch Estates Road N.W., Calgary, Alberta T3G 2B4 (CA). YU, Shuyuan [CA/CA]; 53 Hawktree Circle N.W., Calgary, Alberta T3G 3M1 (CA).

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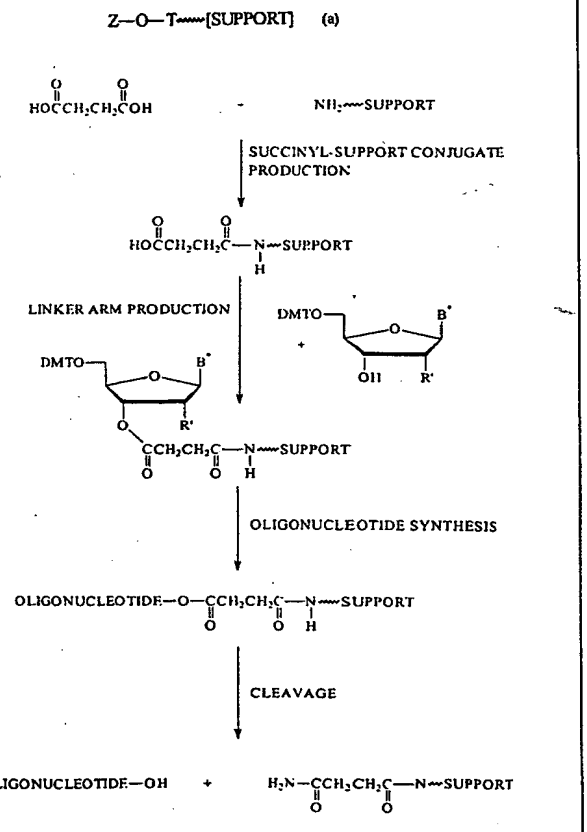
(54) Title: REUSABLE SOLID SUPPORT FOR OLIGONUCLEOTIDE SYNTHESIS

(57) Abstract

A reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising formula (a) wherein Z is a linker moiety and T is an organic radical. A method for adding one or more nucleosides on the linker arm is also described.



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REUSABLE SOLID SUPPORT FOR OLIGONUCLEOTIDE SYNTHESIS

TECHNICAL FIELD

In one of its aspects, the present invention relates to a reusable solid support for oligonucleotide synthesis. In another of its aspects, the present invention relates to a process for production of such a reusable solid support. In yet another of its aspects, the present invention relates to a process for use of such a reusable solid support.

BACKGROUND ART

The art of organic chemistry on solid supports is generally known. A useful review article on this topic may be found in "Organic Chemistry on Solid Supports" by Früchtel et al., *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, pgs. 17-42, the contents of which are hereby incorporated by reference.

As discussed in Früchtel et al., the art has developed automated solid-phase synthesis of polypeptides, oligonucleotides and oligosaccharaides. Of particular interest here is solid-phase synthesis of oligonucleotides. The following are useful review articles/textbooks on this topic:

Beaucage et al., *Tetrahedron*, **1992**, *48*, 2223;
Davis et al., *Innovation and Perspectives in Solid Phase Synthesis* (Ed.: R. Epton), Intercept, Andover, **1992**, pg. 63;
Montserra et al., *Tetrahedron*, **1994**, *50*, 2617; and
S. L. Beaucage et al., *Tetrahedron*, **1993**, *49*, 6123-6194;

the contents of each of which are hereby incorporated by reference.

In the solid-phase synthesis of oligonucleotides, it is known to synthesize the oligonucleotide on an inorganic solid support bearing a succinyl linker arm - see, for example, any of the following references:

Caruthers et al., *Genetic Engineering*, Plenum Press, New York (1982), Vol. 4, pgs. 1-17;

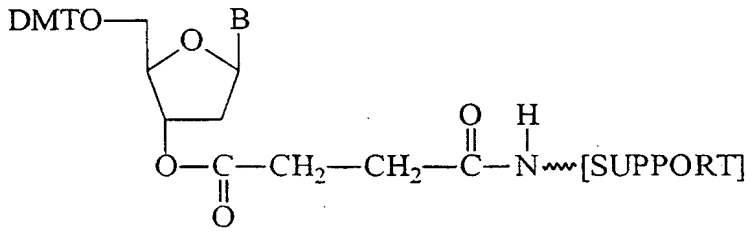
Letsinger et al., *Genetic Engineering*, Plenum Press, New York (1985), Vol. 5, pg. 191;

Froehler et al., *Nucleic Acids Research*, 14:5399-5407 (1986); and

Matteucci et al., *Journal of American Chemical Society*, 103:3185-3186 (1981);

the contents of each of which are hereby incorporated by reference.

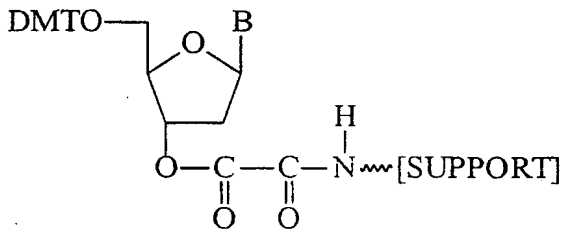
Typically, the succinyl linker arm has the following general formula:



Thus, the succinyl group links the growing oligonucleotide from its terminal 3' hydroxyl group by an ester bond to a primary amine on the support, which may be, for example, conventional controlled pore glass (CPG) or silica, by an amide bond. Once the desired oligonucleotide has been synthesized, it is freed or cleaved from the succinyl linker arm hydrolyzing the ester carbonyl group. The hydrolysis agent is usually concentrated ammonium hydroxide. Typically, this reaction can take from 1-4 hours to complete. With improvements to current solid-phase oligonucleotide synthesizers, this cleavage step can represent 50% or more of the total time require to synthesize the desired oligonucleotide.

Another type of linker arm is disclosed in United States patent 5,112,962 [Letsinger et al. (Letsinger)], the contents of which are hereby incorporated by

reference. Letsinger teaches a linker arm for solid support synthesis of oligonucleotides and oligonucleotide derivatives have the following formula:

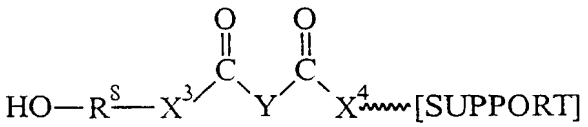


Thus, Letsinger teaches an oxalyl linker arm which purportedly release the synthesized oligonucleotide or oligonucleotide derivate in a period of 1-30 minutes in a manner that leaves the oligonucleotide fully protected. The oxalyl linker arm purportedly can be rapidly cleaved by 5% ammonium hydroxide in methanol, ammonium hydroxide, wet tertiary amine, triethylamine/alcohol, triethylamine/methanol, triethylamine/ethanol, aqueous trimethylamine and other bases. Unfortunately, the oxalyl linker arm of Letsinger suffers from its purported advantage. Specifically, the present inventors have discovered that the oxalyl linker arm of Letsinger is susceptible to significant spontaneous hydrolysis (e.g. spontaneous hydrolysis of ~ 10-40% per month) which renders it difficult to use in commercial operations. The oxalyl arm is also difficult to prepare because it requires using oxalyl chloride, which is highly reactive, toxic and therefore dangerous.

Regardless of the specific nature of the linker arm, it is generally accepted in the art that the linker arm is not reusable after production and cleavage of the desired oligonucleotide. Thus, conventional linker arms may be regarded as non-recyclable. This is illustrated in Figure 1 which illustrates the conventional use of a succinyl linker arm for the production of an oligonucleotide. Thus, as illustrated, after cleavage of the desired oligonucleotide, the support is irreversibly linked to the linker compound (i.e., the succinyl moiety) and cannot be reused.

The art is in need of a linker arm for solid support oligonucleotide synthesis, which linker arm is recyclable. More specifically, the art is in need of a linker arm capable of repeated oligonucleotide synthesis/cleavage.

In published International patent application WO 97/23496 [Pon et al.], the contents of which are hereby incorporated by reference, there is reported the first recyclable linker arm. This linker arm is based on a derivatized solid support having the following formula:

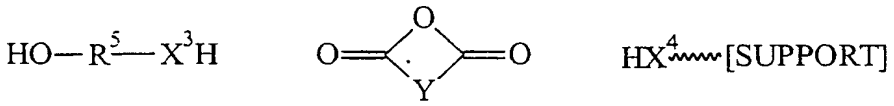


wherein: R^8 is selected from the group consisting of a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5 - C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; X^3 and X^4 are the same or different and are selected from the group consisting of -O-, -S-, -$S(O)_2$- and -$N(R^{12})$-; R^{12} is selected from the group consisting of a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; and Y is selected from the group consisting of:

-CH_2-CH_2-;	-CH_2-;
-CH_2-O-CH_2-;	-CH_2-CH_2-CH_2-;
-CH=CH-;	-CH=C(CH_3)-;
-C(CH_3)=C(CH_3)-;	-CH_2-C(=CH_2)-; and
-CH_2-S-CH_2- .	

While a linker arm based on the solid support described by Pon et al. is a significant advance in the art, there is still room for improvement. Specifically, the solid support described by Pon et al. has the following disadvantages.

First, prior to attachment of the linker moiety, the solid support must be derivatized by a process comprising the step of reacting together the compounds of Formulae I, II and III:



(I) (II) (III)

wherein R^8, X^3, X^4 and Y are as defined above. Practically, this involves two steps - i.e., reaction of the compound of Formula III with one of the compounds of Formulae I and II and subsequent reaction with the other of compounds of Formulae I and II. Thus, the disadvantage is additional labour required to effect a two-step derivatization of the solid support.

Second, each step of the derivatization described in the previous paragraph has the potential of incompletely derivatizing each HX^4- moiety on the support thereby increasing the likelihood of a heterogeneous surface. Practically, it becomes necessary to block or cap underivatized HX^4- moieties so that the linker moiety does interact with them. Thus, the disadvantage is additional labour and cost required to effect derivatization of the solid support.

Third, a linker arm based on the derivatized support described by Pon et al. is not as resistant to partial cleavage during regeneration as a derivatized support having a more fully saturated moiety.

In light of these disadvantages, it would be desirable to have an improved recyclable solid state support material useful in the oligonucleotide synthesis. It would be especially desirable if the the linker moiety could be attached to the support material with little or no derivatization required of the latter.

DISCLOSURE OF THE INVENTION

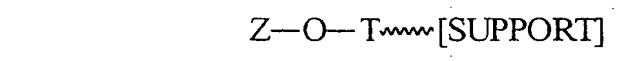
It is an object of the present invention to provide a novel solid support for oligonculeotide synthesis which obviates or mitigates at least one of the above-mentioned disadvantages of the prior art.

It is another object of the present invention to provide a novel process for producing the solid support.

It is an object of the present invention provide a novel linker arm for solid support oligonucleotide synthesis which obviates or mitigates at least one of the above-mentioned disadvantages of the prior art.

It is another object of the present invention to provide a novel process for producing a linker arm for solid support oligonucleotide synthesis.

Accordingly, in one of its aspects, the present invention provides a reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising the following formula:

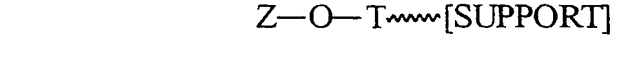


wherein Z is a linker moiety and T is an organic radical.

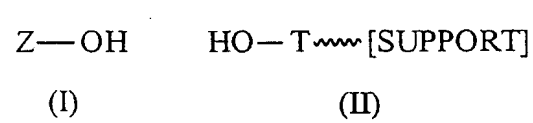
In another of its aspects, the present invention provides a reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising the following formula:

wherein Z is a linker moiety and T is an organic radical.

In yet another of its aspects, the present invention provides a process for production of a reusable linker arm for oligonucleotide synthesis having the following formula:



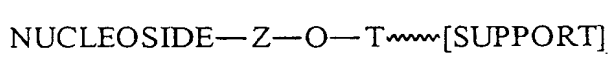
wherein Z is a linker moiety and T is an organic radical, the process comprising the step of reacting together the compounds of Formulae I and II:



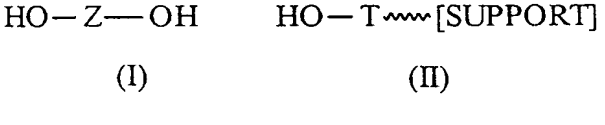
(I) (II)

wherein Z and T are as defined above.

In another of its aspects, the present invention provides a process for production of a reusable linker arm for oligonucleotide synthesis having the following formula:



wherein Z is a linker moiety and T is an organic radical, the process comprising the step of reacting together the compound of Formulae I, II and III:



(I) (II)

(III)

wherein Z and T are as defined above.

In yet another of its aspects, the present invention provides a process for producing an oligonucleotide having a desired sequence comprising the steps of:

(i) reacting a linker arm having the formula:

NUCLEOSIDE—Z—O—T~~~[SUPPORT]

wherein Z is a linker moiety and T is an organic radical, with at least one oligonucleoside base until an oligonucleotide having the desired sequence is produce;

(ii) cleaving the oligonucleotide having the desired sequence to produce a free oligonucleotide have the desired sequence; and a used linker arm; and

(iii) recycling the used linker arm to Step (i).

As used throughout this specification, the term "oligonucleotide" is intended to have a broad meaning and encompasses conventional oligonucleotides, backbone-modified oligonucleotides (e.g. phosphorothioate, phosphorodithioate and methyl-phophonate analogs useful as oligotherapeutic agents) and oligonucleotide derivatives such as oligonucleotide-peptide conjugates.

Throughout this specification, when reference is made to a substituted moiety, the nature of the subsitution is not specification restricted and may be selected from the group consisting of a C_1-C_{20} alkyl groups, aC_5-C_{30} aryl group a C_5-C_{40} alkaryl group.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present invention will be described with reference to the accompany drawing in which:

Figure 1 illustrates a specific process pathway for conventional oligonucleotide synthesis; and

Figures 2 and 3 illustrate specific preferred embodiments of the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

Initially, to facilitate an understanding of the invention, reference will be made to Figure 1, which illustrates a conventional process for solid support oligonucleotide synthesis.

Thus, the initial step of the process illustrated in Figure 1 comprises reacting a linking compound, such as succinic acid (while succinic acid is illustrated, succinic anhydride may also be used), with a conventional amine-terminated support. The reaction results in the formation of an amide linkage between the linking compound and the support to produce succinyl-support conjugate.

Next, the succinyl-support conjugate is reacted with a desired initial nucleoside to produce a linker arm. In the illustrated nucleoside, DMT is dimethyoxytrityl, B is the nucleobase and R' is H (for deoxyribonucleosides) or OR (for ribonucleosides) wherein R is H or a conventional blocking/ protecting group. The reaction results in the formation of an ester linkage between the linking compound and the desired initial nucleoside at the 3' position of the latter.

The linker arm is then used in conventional oligonucleotide synthesis (e.g. in a conventional automated synthesizer) to produce an oligonucleotide of desired sequence attached to the linker arm.

The oligonucleotide is then cleaved from the linker by hydrolysis. This serves to cleave the ester bond thereby freeing the oligonucleotide and an amine-terminated, non-reusable linker arm.

The present inventors have surprisingly and unexpectedly discovered that a support having a hydroxy-terminated functionality may be combined with a conventional linking compound to produce linker arm which may used to synthesize an oligonucleotide of desired sequence. A key feature of the invetion is that the linker arm may be regenerated or recycled after cleavage of the oligonucleotide of desired sequence. To the inventors' knowledge, this is the first discovery of a derivatized support which may be used repeatedly in oligonucleotide synthesis.

The reusable linker arm of the present invention has the following formula:

Z—O—T~~~[SUPPORT]

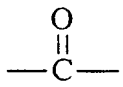
wherein Z is a linker moiety and T is an organic radical.

Preferably, T contains at least one carbon.

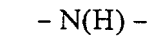
Preferably, T is a C_1-C_{300} organic moiety, more preferably a C_1-C_{200} organic moiety, most preferably a C_1-C_{100} organic moiety.

As will be appreciated by those of skill in the art, T may be a saturated or unsaturated organic moiety. Further, T may contain one or more heteroatoms. For example, T may comprise at least one heteroatom selected from N and O.

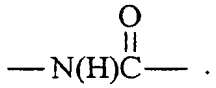
In one preferred embodiment, the organic moiety in T comprises at least one moiety having the formula:



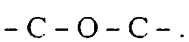
In another preferred embodiment, the organic moiety in T comprises at least one moiety having the formula:



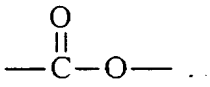
In yet another preferred embodiment, the organic moiety in T comprises at least one moiety having the formula:



In yet another preferred embodiment, the organic moiety in T comprises at least one moiety having the formula:

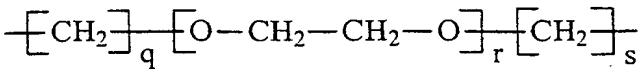


In yet another preferred embodiment, the organic moiety in T comprises at least one moiety having the formula:



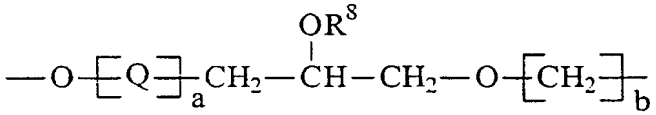
Further, those of skill in the art will recognize that the organic moiety in T may be unsubstituted or substituted. For examples, the organic moiety of T may be substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

In one preferred embodiment, T has the formula:



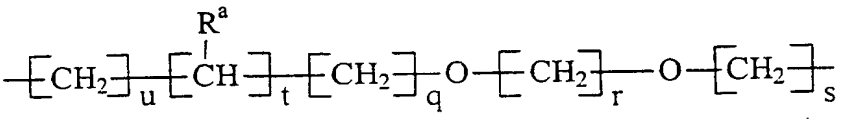
wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200. In this embodiment, it is further preferred that q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.

In another preferred embodiment, T has the formula:



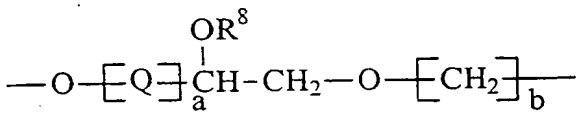
wherein a is 0 or 1, Q is an organic moiety, R^8 is hydrogen or a protecting group and b is an integer having a value of 0-40. In this embodiment, a may be 0 and R^8 may be hydrogen. Further, a may be 1 and R^8 may be a protecting group. Non-limiting examples of protecting groups may be selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyl-dimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, acetyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenyl-methoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-methoxypiperidinyl and mixtures thereof.

In this embodiment, Q may be a moiety having the formula:



wherein q, r, s, t and u are the same or different and each is an integer having a value of 0-40 and R^a is selected from the group comprising hydrogen, hydroxyl, a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group. Preferably, s is 0, q, r and u are the same or different and each is an integer having a value of 1-10, t is an integer of 1-5 and R^a is hydroxyl.

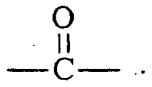
In yet another preferred embodiment, T has the formula:



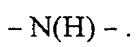
wherein a is 0 or 1, Q is an organic moiety, R^8 is selected from the group comprising hydrogen, hydroxyl, a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group, and b is an integer having a value of 0-40. Preferably, Q is a C_1-C_{100} organic moiety. As will be appreciated by those of skill in the art, Q may be a saturated organic moiety or an unsaturated organic moiety.

It is preferreed that Q is a C_1-C_{100} organic moiety comprising at least one heteroatom selected from N and O.

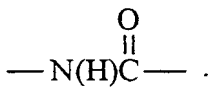
In one preferred embodiment, the organic moiety Q comprises at least one moiety having the formula:



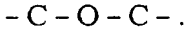
In another preferred embodiment, the organic moiety Q comprises at least one moiety having the formula:



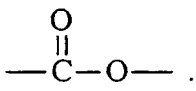
In yet another embodiment, the organic moiety Q comprises at least one moiety having the formula:



In yet another embodiment, the organic moiety Q comprises at least one moiety having the formula:

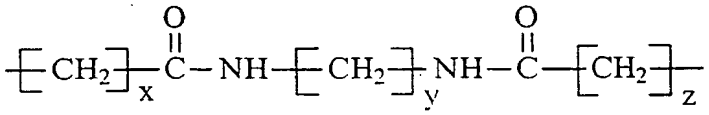


In yet another embodiment, the organic moiety comprises at least one moiety having the formula:



As will be appreciated by those of skill in art, the organic moiety Q may unsubstituted or substituted. For example, the organic moiety Q may be substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

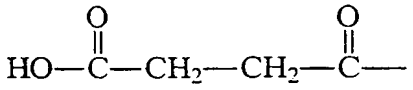
In one preferred embodiment, Q has the formula:



wherein each of x, y and z is an integer having a value of 1-40.

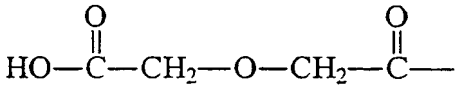
In the above formula for the present linker arm, Z is a linker moiety. As will be discussed below, Z is derived from a linker compound have the general formula HO-Z-OH (Formula I below). The nature of the linker compound is not particularly restricted.

In one preferred embodiment, linker moiety Z has the formula:



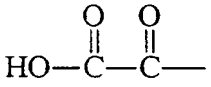
As will be apparent to those of skill in the art, this linker moiety may be derived from succinic acid or succinic anhydride.

In another preferred embodiment, linker moiety Z has the following formula:



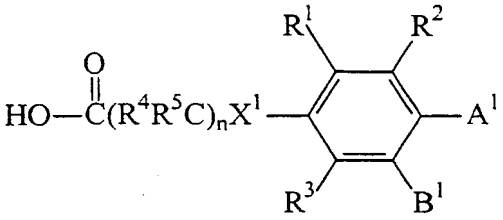
As will be apparent to those of skill in the art, this linker moiety may be derived from diglycolic acid or diglycolic anhydride.

In yet another preferred embodiment, linker moiety Z has the following formula:



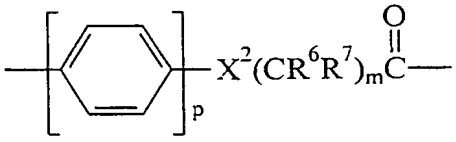
As will be apparent to those of skill in the art, this linker moiety may be derived from oxalic acid or oxalyl chloride.

In yet another, and most, preferred embodiment, linker moiety Z has the following formula:



wherein: R^1, R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted

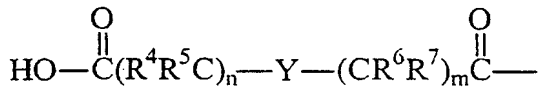
C_5-C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -C(O)-, -S-, -$S(O)_2$- and -N(R)-; R is selected hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:



wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, R^6 and R^7 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and m is 0, 1 or 2. In this embodiment, B^1 preferably is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group. Preferably, at least one, more preferably each, of R, R^4, R^5, R^6 and R^7 is hydrogen and preferably at least, more preferably both, of m and n are 1. It is further preferred that each of R^1, R^2 and R^3 is hydrogen and that X^1 and X^2 are both -O-. Thus, in this embodiment, the most

preferred form of linker moiety Z is derived from hydroquinone-O,O'-diacetic acid.

In yet another preferred embodiment, linker moiety Z has the following formula:



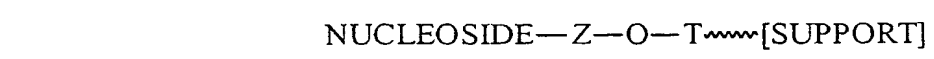
wherein R^4, R^5, R^6 and R^7 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, Y is selected from the group consisting of O, S, SO_2 and $O-((CH_2)_l-O)_q$, l is an integer less than or equal to 60, q is an integer in the range of 1-1000, n and m are the same or different and are 1 or 2, with the proviso that, when Y is O, at least one of n and m is 2. Preferably, l is an integer in the range of 1-10, and q is an integer in the range of 1-1000. In this embodiment, the most preferred form of linker moiety Z is derived from thiodiglycolic acid (i.e. R^4=R^5= R^6=R^7=H, n=m=1 and Y=S).

The SUPPORT in the above formula is a conventional solid support. The nature of the solid support is not particularly restricted and is within the purview of a person skilled in the art. Thus, the solid support may be an inorganic substance. Non-limiting examples of suitable inorganic substances may be selected from the group consisting of silica, porous glass, aluminosilicates, borosilicates, metal oxides (e.g. aluminum oxide, iron oxide, nickel oxide) and clay containing one or more of these. Alternatively, the solid support may be an organic substance such as a cross-linked polymer. Non-limiting examples of a suitable cross-linked polymer may be selected from the group consisting of polyamide, polyether, polystyrene and mixtures thereof. The preferred solid support for use herein is conventional and may be selected from controlled pore glass bead or polystyrene beads. Further, the support may be either in particle

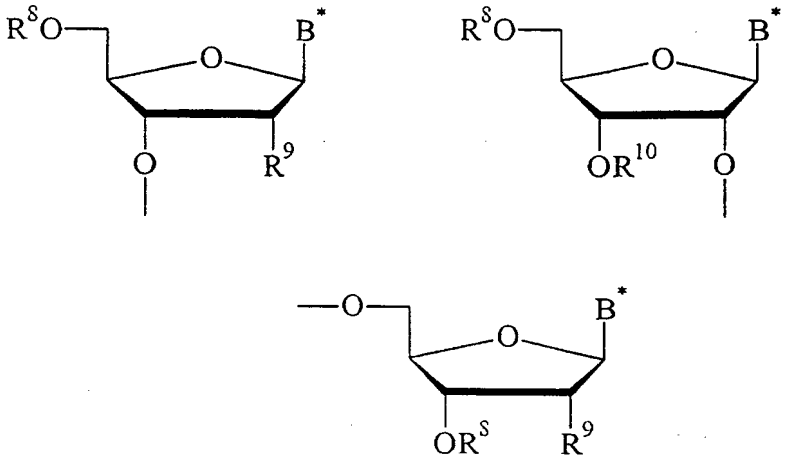
form (e.g., beads), three-dimensional slabs (e.g., polymeric inserts and foams) or in a flat two-dimensional like format (e.g., plastic sheets, glass chips, silicon wafers, etc.). The material used for the support may also be soluble in certain solvents (e.g., liquid-phase supports), but can be precipitated or crystallized from other solvents.

The reusable linker of formula:

(again, Z is a linker moiety and T is an organic radical), may then be reacted with a conventional nucleoside-linker compound to produce another linker arm according to the present invention. This other linker arm has the following formula:



wherein Z is a linker moiety and T is an organic radical. The discussion herein above with respect to Z and T applies equally here. Preferably, in the above formula, NUCLEOSIDE is a moiety selected from one of the following formulae:



wherein R^8 and R^{10} are the same or different and are hydrogen or a protecting group, R^9 is hydrogen (for deoxyribonucleosides or DNA) or $-OR^{11}$ (for ribonucleosides or RNA) wherein R^{11} is hydrogen or a protecting group, and B^* a nucleic acid base. Thus, in the case of RNA, there are two hydroxyl groups which may be protected. Also, the linker can be attached to either the 5'-, 3'- or (if ribose) 2'- hydroxyl positions. Indeed, for RNA sequences, it makes little difference whether the ester linker formed between the nucleoside and the linker compound is at the 2'- or 3'- hydroxyl position of the nucleoside. Thus, those of skill in the art will recognize that the nucleoside may be protected or blocked at the various of its hydroxyl moieties.

Non-limiting examples of useful protecting groups may be selected from the group consisting of acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyldimethylsilyl,

diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, acetyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenyl-methoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-methoxypiperidinyl and the like.

As is known in the art, the main prerequisite for the protecting group used on the 5'-hydroxyl position is its ability to be selectively removed without causing cleavage of the linker arm. Thus, the preferred protecting group for desired 5'-hydroxyl position(s) is the acid labile dimethoxytrityl group. The main prerequisite for protecting groups on other hydroxyl positions, is stability to the conditions used for removal of the above protecting group. These latter protecting groups may be removed by the same conditions used to cleave the linker (discussed below) or separate conditions. The preferred protecting groups for these positions are trialkylsilyl (i.e. t-butyldimethylsilyl) or acetyl. Additional information may be obtained from the following references:

1. T. W. Greene and P. G. M. Nuts, "Protecting Groups in Organic Synthesis", Second Edition (1991), John Wiley and Sons, Inc., NY;
2. M. Schelhaas and H. Waldman, "Protecting Group Strategies in Organic Synthesis", Angew. Chemie Int. Ed. Engl. **35**, 2056-2083 (1996);
3. M. J. Gait, ed., "Oligonucleotide Synthesis A Practical Approach", IRL Press, Oxford (1984);
4. S. A. Narang, ed., "Synthesis and Applications of DNA and RNA", Academic Press, Inc., Orlando (1987); and
5. S. Agrawal, ed., "Methods in Molecular Biology, Vol. 20: Protocols for Oligonucleotides and Analogs", Humana Press, Totowa, NJ (1993);

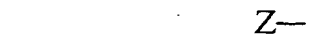
the contents of each of which are hereby incorporated by reference, for a discussion of other possible hydroxyl protecting groups.

The manner by which the desired nucleoside may be protected is conventional and within the purview of a person skilled in the art. See, for example United States patent 3,400,190 (Melby), United States patent 4,458,066 (Caruthers et al.), the contents of each of which are hereby incorporated by reference.

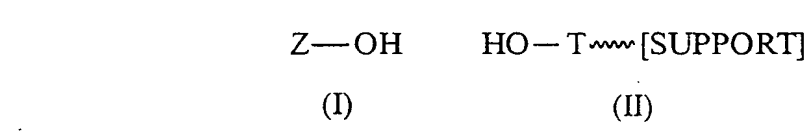
A preferred method for production of deoxyribonucleosides in the context of the present invention is to use a nucleoside with a 5'-dimethoxytrityl protecting group and an appropriate exocyclic amino protecting group, e.g., N^6-benzoyl-5'-dimethoxytrityl-2'-deoxyadenosine, N^4-benzoyl-5'-dimethoxytrityl-2'-deoxycytidine, 5'-dimethoxytrityl-N^2-isobutyryl-2'-deoxyguanosine, or 5'-dimethoxytritylthymidine.

A preferred method for production of ribonucleosides in the context of the present invention is to use a 5'-dimethoxytrityl protected nucleoside, with appropriate exocyclic amino protection, and no protecting groups on either of the 2'- or 3'- hydroxyl positions. The linker can then react with either one of the two adjacent hydroxyl groups (it doesn't matter which) to give a mixture of 2'- and 3'-linkages. The unreacted hydroxyl groups may then be acetylated by treatment of the immobilized nucleoside with acetic anhydride. Alternatively, ribonucleosides which have a 5'-dimethoxytrityl group, appropriate exocyclic amino group protection, and either a 3'-hydroxyl protecting group or a mixture of 2'- and 3'-protecting groups can be used. The 3'-protected compounds are generally unwanted isomers which are simultaneously produced when the 2'-hydroxyl position is protected and having little other use.

The reusable linker arm having the formula:



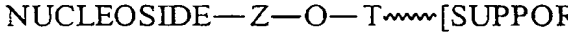
may be produced by a process comprising the step of reacting together the compound of Formulae I and II:



(I) (II)

wherein Z and T are as defined above.

The reusable linker arm having the formula:



comprises the step of reacting together the compounds of Formulae I, II and III:

(I) (II)

(III)

wherein Z and T are as defined above.

The compounds of Formulae I and II or of Formulae I, II and III (depending on which version of the present linker arm is being produced) are preferably reacted in the presence of an activating agent. As used throughout this specification, the term "activating group" is intended to have a broad meaning and is intended to encompass electrophilic reagents capable of activating a

carboxyl moiety (e.g., on the linking compound of Formula II) by attachment of a leaving group to the acyl carbon of the carboxl moiety - see, for example, M. Bodanszky, "Principles of Peptide Synthesis", Second Edition, Springer-Verlag, Berlin (1993), the contents of which are hereby incorporated by reference. Thus, the activating agent should be capable of initiating at least one of the following: (a) formation of a reactive acylating agent (this is an example of a derivate) from the carboxyl moeiy in a separate step or steps, followed by immediate treatment with the amino component (in this case, for example, an amino-terminated support) to form an amide linkage or a hydroxy component (in this case a hydroxy-terminated support or a hydroxyl group on the desired nucleoside) to form an ester linkage; (b) formation of an isolable acylating agent, separately, optionally with purification prior to treatment with the amino or hydroxy component as discussed in (a); and (c) formation of an acylating intermediate in the presence of the amino/hydroxy component, by the addition of an activating agent to a mixture of the two components. Thus, each of (a), (b) and (c) are applicable to the formation of both carboxylic esters and amides and all three routes can be used to attach nucleosides to supports.

For example, the Letsinger method, which first reacts oxalyl chloride with triazole, and then adds a nucleoside to the resulting oxalyl triazolide is an example of route (a). Conversion of the carboxylic acid group into an "active" ester using either p-nitrophenol, or di-, tri-, tetra-, or penta- chlorinated or fluorinated phenols, or N-hydrosuccinimide are common examples of route (b). Route (c) has been the most commonly used method in recent years and both the carbodiimide reagents (dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-ethylcarbodiimide, and diisopropylcarbodiimide) and uronium reagents (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, (HBTU)) may be used in this approach.

In a preferred embodiment, in addition to an activating reagent, the reaction of the compounds of Formulae I, II and III is conducted in the presence of a nucleophilic catalyst or additive (typically 4-dimethylamino pyridine (DMAP), 1-hydroxybenzotriazole (HOBt), or 1-hydroxy-7-azabenzotriazole

(HOAt)) to speed up the reaction and a tertiary amine base (typically triethylamine, pyridine, or diisopropylethylamine) to ionize the carboxylic acid group.

Thus, those of skill in the art will recognize that the precise nature of the activation agent is not particularly restricted provided, of course, that the activated carboxylic acid group is capable of initiating formation of the ester or amide linkage, as appropriate, and the activating reagent does not have any deleterious effect on the desired nucleoside.

Thus, activation of the carboxylic acid by conversion into an acid chloride; an active ester (i.e., nitrophenyl, nitrophenylthio, trichlorophenyl, trifluorophenyl, pentachlorophenyl, pentafluorophenyl, or 3-hydroxy-2,3-dihydro-4-oxo-benzotriazine esters); an active hydroxylamine ester (i.e., N-hydroxyphthalimide or N-hydroxysuccinimide); acid anhydride; or mixed anhydride will produce derivates which will form the desired linkage, and thus, these strategies are encompassed herein.

Non-limiting examples of activating agents may be selected from the group consisting of arylsulfonyl chlorides (e.g., benzenesulfonyl chloride (BS-Cl), mesitylenesulfonyl chloride (MS-Cl), triisopropylsulfonylchloride (TPS-Cl)); active arylsulfonyl esters (i.e., imidazole, triazole, nitrotriazole, or tetrazole esters of BS-Cl, MS-Cl or TPS-Cl); 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ); acyl carbonates; 1,1'-(carbonyldioxy)dibenzotriazoles; chlorotrimethyl-silane; carbodiimides (i.e., dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-ethylcarbodiimide (DEC), diisopropylcarbodiimide (DIC)) either alone or in combination with auxillary nucleophiles (i.e., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (i.e., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)); or uronium salts (i.e., tetramethyluronium chloride (TMU-Cl), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), 2-(3,4-dihydro-4-oxo-1,2,3-

benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDBTU), 2-(2-oxo-1(2H)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate (HAMDU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (HAMTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate (HApipU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate (HAPyU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)) either alone or in combination with auxillary nucleophiles (i.e., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g. 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)) or phosphonium salts (e.g. benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP), 2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate (BOI), bromo tris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP), 7-azabenzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (AOP), and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)) either alone or in combination with auxillary nucleophiles and/or catalysts (discussed above) will also produce the desired linkage.

Other examples of suitable activating reagents may be found in any of the following references:

M. Bodanszky, "Principles of Peptide Synthesis", Second Edition, Springer-Verlag, Berlin (1993);

J. Jones, "Amino Acid and Peptide Synthesis", Oxford University Press, Oxford (1992);

G. Grant, "Synthetic Peptides: A Users Guide", W. H. Freeman & Co., NY (1992);

E. Haslam, Tetrahedron, 36, pg. 2409, (1980); and

M. A. Ogliaruso and J. F. Wolfe, "Synthesis of Carboxylic Acids, Esters and Their Derivatives", John Wiley & Sons, Chicester (1991);

the contents of each of which are hereby incorporated by reference.

In producing the present linker arm, the order of reaction is not particularly restricted. Thus, in one embodiment (this is the preferred embodiment), the compounds of Formulae I and III are initially reacted to form a conjugate which is reacted with the compound of Formula II. In another embodiment, the compounds of Formulae I and II are initially reacted to form a conjugate which is reacted with the compound of Formula III.

The addition of compounds of Formulae I and III to Formula II, usually will not result in the quantitative conversion of each immobilized hydroxyl group into a derivatized ligand. Therefore, it is preferred that unreacted hydroxyl groups on the surface of the support be protected (capped) by reaction with a capping reagent. This will mitigate the free hydroxyl group participating in subsequent oligonucleotide chain extension reactions, resulting in defect sequences lacking the terminal nucleoside. Preferably, the capping reagent should be reversible so that the capping agent can be removed to regenerate the hydroxyl sites prior to the next round of support derivatization. Capping of the unreacted sites is conventional and can be performed by reaction with an activated carboxylic acid or anhydride to form an ester, or by addition of a protecting group, as described hereinabove. Thus, for example, t-butylphenoxyacetic anhydride, methoxyacetic anhydride or preferably chloroacetic anhydride, combined with 2,6-lutidine and N-methylimidazole in THF solution are useful examples of capping reagents.

With reference to Figure 2 there is illustrated a preferred pathway illustrating the use of the present linker arm in a recycled/regenerated manner. In Figure 2, DMT refers to dimethoxytrityl and B refers to a nucleobase as described hereinabove. As will be apparent to those of skill in the art, the support is recycled after oligonucleotide cleavage and support regeneration to a point in

the reaction scheme where it may again be coupled with the HQPD-nucleoside conjugate for further oligonucleotide synthesis.

With further reference to "Oligo Synthesis" (Step #3) in Figure 2, once the present linker arm has been produced, it may be used in the conventional manner to synthesize an oligonucleotide - see, for example, United States patent 5,112,962 (Letsinger), incorporated by reference hereinabove. Once the oligonucleotide has been synthesized, it may be cleaved from the solid support to yield the free oligonucleotide and the support may then be regenerated - see Step #4 of Figure 2.

The cleavage step comprises hydrolysis at the point of attachment of the initial nucleoside to the linking compound. The regeneration of the support involves the removal of two moieties: (i) the removal of the structure represented by Formula I (above) from Formula II (above), which occurs simultaneously with the release of the oligonucleotide product, and (ii) the removal of the moiety used to protect (cap) unreacted hydroxyl sites of Formula II (above) on the support. Removal of these two moieties can occur simultaneously or separately to regenerate the support. Simultaneous removal of both moieties using only a single reagent is simpler but care should be taken to use reagents which will not deleteriously affect the oligonucleotide product. A two-step regeneration involving the removal of the oligonucleotide using one reagent (typically ammonium hydroxide) and then treatment of the support with a second reagent (which may be faster but otherwise damaging to the oligonucleotide product thereby necessitating use of a two-step regeneration) allows flexibility in the choice of capping and regeneration reagents.

The reagent used to effect cleavage is not particularly restricted and is within the purview of a person skilled in the art. Preferably, the reagent is a base mild enough not to damage the oligonucleotide product but sufficiently strong to effect rapid cleavage. Non-limiting examples of suitable reagents for this purpose may be selected from the group consisting of ammonium hydroxide, ammonium hydroxide/methanol, ammonia/methanol, ammonium hydroxide/methylamine, potassium carbonate/methanol, t-butylamine, ethylenediamine, methylamine, dimethylamine, trimethylamine/water and the like. Cleavage may also be

performed under neutral conditions using fluoride ion (i.e. 1M tetrabutylammonium fluoride/THF or triethylamine trihydrofluoride). The reagent used to remove the capping reagent from unreacted sites may consist of the above reagents or other stronger bases such as sodium or potassium hydroxide. In our preferred embodiment, ammonium hydroxide can be used to cleave the oligonucleotide product from the support, remove the HQPD linker arm, and cleave chloroacetyl protected hydroxyl groups in a single regeneration step. The preferred temperature for the cleavage and regeneration is room temperature, but higher or lower temperatures can be employed, subject to the limitations of the apparatus used.

With reference to Figure 3, there are illustrated specific preferred examples of hydroxyl reusuable linker arms falling within the scope of the present invention.

Embodiments of the invention will be illustrated in the following Examples which should not be construed as limiting the scope of the invention. In the Examples, the following materials were used:

1. Long chain alkylamine (LCAA) or glycerol (Gly) derivatized controlled pore glass (CPG) beads (120/200 mesh) were obtained from CPG Inc (Lincoln Park, NJ);

2. Toyopearl AF-amino-650M and HW65F supports were obtained from TosoHaas (Montgomeryville, PA);

3. Other supports were obtained from the manufacturers listed in Tables 1 and 2;

4. HQPD, Hydroquinone-O,O'-diacetic acid, commercially available from Lancaster Synthesis Ltd. (Lancashire, England);

5. Ammonium hydroxide solutions (28-30%) and solvents were obtained from VWR Canlab (Edmonton, Alberta, Canada);

6. Capping solutions were formulated as either Cap A (acetic anhydride/2, 6-lutidine/THF in a volume ratio of 1:1:8) and Cap B (N-methylimidazole and THF in a volume ratio of 16:84) or Cap A (chloroacetic anhydride and THF, 17% by weight) and Cap B (2, 6-lutidine and N-methylimidazole in THF in a volume ratio of 12:16:72);

7. Anhydrous pyridine and acetonitrile, distilled from CaH_2;

8. DIEA, diisopropylethylamine, reagent grade;

9. MeCN, acetonitrile, low water DNA synthesis grade;

10. DMAP, 4-dimethylaminopyridine, reagent grade;

11. DEC, 1-(3-dimethylaminopropyl)-ethylcarbodiimide, reagent grade;

12. Sulfurizing reagent, Beaucage thiolating reagent, from Pharmacia Biotech, was used as a 0.05M solution in acetonitrile; and

13. HBTU, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate, reagent grade;

In the following Examples the amount of nucleoside (loading) on the insoluble supports was determined by spectrophotometric trityl analysis. In this procedure, a sample of support (4-5 mg) was accurately weighed directly into a 10 mL volumetric flask. A solution of dichloroacetic acid in 1,2-dichloroethane in a volume ration of 5:95 was then added to fill the flask. The contents were then thoroughly mixed and the absorbance of the orange coloured solution was measured at 503 nm using a Philips UV/Vis spectrophotometer. The nucleoside loading (in μmol/g of CPG) was then calculated as:

$$\text{Loading} = (A_{503} \times \text{Vol} \times 1000) / (\text{Wt} \times 76)$$

wherein A_{503} = absorbance at 503 nm, Vol = solution volume in mL, and Wt = amount of CPG tested in mg. The accuracy of the trityl determination was approximately ± 2-3%.

Example 1 - SYNTHESIS OF NUCLEOSIDE-3'-*O*-HQDA HEMIESTERS

5'-Dimethoxytrityl-N-protected deoxyribonucleoside (10 mmol), hydroquinone-*O,O'*-diacetic acid (15 mmol, 3.39 g), 4-dimethylaminopyridine (1 mmol, 122 mg), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15 mmol, 2.88 g) were combined in a 100 mL round bottom flask equipped with a magnetic stir bar. Triethylamine (0.8 mL) and anhydrous

pyridine (50 mL) were added to the flask and the contents were stirred at room temperature overnight.

The reaction was checked by TLC (5% methanol/chloroform). If more than a trace of starting nucleoside was visible, more 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2-5 mmol) was added to the reaction and stirring was continued for another day. When TLC showed complete disappearance of the starting nucleoside, the solution was concentrated by evaporation until a thick oil was formed. The oil was redissolved in chloroform (~ 200 mL) and transfer to a separatory funnel. The chloroform solution was washed with aqueous sodium bicarbonate (~ 100 mL x 2) and then water (~ 100 mL x 3). The funnel was slowly inverted to mix the two phases. The chloroform phase was collected and the aqueous phase was discarded. If an inseparable emulsion was formed, then either centrifugation (for small volumes) or (for large volumes) precipitation by addition of hexanes followed by filtration and redissolving the sticky precipitate back into chloroform can be performed.

The chloroform solution was added to anhydrous magnesium sulfate and mixed to remove residual moisture from the solution. The magnesium sulfate was filtered off, the filtrated was washed with a small amount of chloroform and then the chloroform solution was evaporated to dryness. A light brown foam, containing a mixture of diester and nucleoside hemiester sodium salt, was formed and solidified.

The hemiester sodium salt was converted into a more soluble pyridinium salt by dissolving the foam in pyridine (~ 50-100 mL) and then adding AG 50W-X4 H^+ cation exchange resin (2 eq.). The mixture was stirred for approximately 5 minutes and then the ion exchange resin was filtered off. The pyridine solution was evaporated to dryness. A light brown foam formed and solidified. The sold was dried under vacuum overnight to remove excess pyridine.

Example 2 - PREPARATION OF 12-DIMETHOXYTRITYL-HYDROXYDO-DECANOIC ACID DERIVATIZED SUPPORTS

This example describes the synthesis of a C_{12} linker arm within the scope of the present invention and how it can be used to convert commercially available amino-derivatized supports into reusable hydroxyl-derivatized supports.

12-Hydroxydodecanoic acid (9.25 mmol) was coevaporated to dryness with pyridine (3x). Then pyridine (~ 40 mL) and dimethoxytrityl chloride (10.2 mmol) were added. After stirring overnight, the solution was concentrated (to 10 mL), diluted with $CHCl_3$ (50 mL), washed with aq. NH_4HCO_3 (3x) and water (2x). The crude material was then purified on a silica gel column by elution with a 1% TEA/$CHCl_3$ – 4% MeOH/1%TEA/$CHCl_3$ gradient. The prodcut yield was 6.7 mmol (72%) of 12-dimethoxytrityl-hydroxydodecanoic acid as a brown oil.

An amino functionalized support (0.5 g), 12-dimethoxytritylhydroxy-dodecanoic acid (0.2 mmol), 4-dimethylaminopyridine (0.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 mmol), triethylamine (0.1 mL), and pyridine (7 mL) were shaken at room temperature (16 h). The support was filtered off, washed, and dried. Linker loading was determined by trityl analysis and the results are provided in Table 1. Unreacted amino and hydroxyl groups on the derivatized support (if present) were then acetylated by treating the support with equal volumes 1 M acetic anhydride/2,6-lutidine/THF (Cap A) and 2M N-methylimidazole/THF (Cap B) reagents for 3 hours. The support was then filtered off, washed, and dried.

Table 1- Loading Results Using 12-Dimethoxytrityl-hydroxydodecanoic Acid Linker Arm

Experiment	Support	Linker arm loading (μmol/g)
1	Pharmacia HL-30 amino primer support	216
2	Long chain alkylamine CPG	87
3	Amino Tentagel, Millipore	107
4	Toyopearl AF-amino-650M	217
5	Aminoethyl polystyrene, Hamilton	73
6	Aminomethyl polystyrene, Applied Biosystems	28

Example 3 - DERIVATIZATION OF TOYOPEARL HW-65F SUPPORT WITH 1,4-BUTANEDIOL DIGLYCIDYL ETHER

This Example describes how hydroxyl surface groups on commercially available Toyopearl HW65 supports are extended with a butane diglycidyl linker to create a reusable support.

Toyopearl HW-65F vinyl alcohol/methacrylic acid copolymer was obtained as a slurry in 500 ml 20% ethanol/water. This slurry was evaporated to dryness to yield of 90 g of dry support. The hydroxyl content of the dry support was determined, in triplicate, by derivatization with dimethoxytrityl chloride/tetrabutylammonium perchlorate and trityl analysis, to be 1,095 μmol/g.

The dry HW-65F support (25 g), 1.0 M aqueous NaOH solution containing 1 mg/mL $NaBH_4$ (100 mL) and 1,4-butanediol diglycidyl ether (75 mL) were shaken at room temperature (3.5 h). The support was filtered off and washed with water, acetonitrile, and then chloroform. After drying, DMT derivatization and analysis (M.P. Reddy and P.J. Voelker, 1988, Int. J. Peptide Protein Res. **31**, 345-348, the contents of which are hereby incorporated by reference) of a sample indicated 902 μmol/g of remaining hydroxyl groups. Therefore, the epoxide loading was estimated to be 193 μmol/g.

The epoxide derivatized support (25 g), benzoic anhydride (51 g), 4-dimethylaminopyridine (6.6 g) and anhydrous pyridine (180 mL) were shaken at room temperature (overnight) to benzoylate unreacted hydroxyl groups. The support was filtered off, washed (methanol, then chloroform), and dried. DMT derivatization and analysis indicated that the residual hydroxyl group loading had decreased to only 5 μmol/g.

The benzoylated support (25 g), THF (140 mL), and 2.9 N aqueous $HClO_4$ (16.6 mL, 48 mmol) were shaken at room temperature (13 h). Trityl derivatization and analysis of an aliquot showed an hydroxyl loading of 98 μmol/g. Additional 2.9 N $HClO_4$ (34 mL) was added and shaking continued for another 3 h. The support was filtered off, washed, and dried and a final trityl derivatization and analysis indicated an hydroxyl loading of 103 μmol/g.

Example 4 - SYNTHESIS OF OLIGONUCLEOTIDE PHOSPHOROTHIOATES AND SUPPORT RECYCLING USING CHLOROACETIC ANHYDRIDE CAPPING.

This Example provides experiments which illustrate the suitability of a variety of different supports for repetitive oligonucleotide synthesis.

The following reagents were installed on a Perkin-Elmer/Applied Biosystems 394 4-column, 8-base position DNA synthesizer:

Ports #1-4: dA^{Bz}, dG^{iBu}, dC^{Bz}, and T phosphoramidites (0.2 M solutions).

Port #7: 0.15 M 5'-dimethoxytrity-N^6-benzoyl-2'-deoxyadenosine-3'-*O*-hydroquinone-*O,O'*-diacetyl hemiester pyridinium salt and 0.15 M diisopropylethylamine in anhydrous acetonitrile.

Port #8: 0.15 M HBTU and 0.15M DMAP in anhydrous acetonitrile.

Port #9: 0.45 M Tetrazole/acetonitrile.

Port #10: 28% Ammonium hydroxide.

Port #11: 1 M Chloroacetic anhydride in THF (Cap A reagent).

Port #12: 1 M 2,6-Lutidine and 2 M N-methylimidazole in THF (Cap B reagent).

Port #14: 5% (v/v) Dichloroacetic acid/1,2-dichloroethane.

Port # 15: 0.05 M Beaucage reagent in acetonitrile.

Up to four synthesis columns, each containing one of the supports listed in Table 2, were installed on the synthesizer and, if necessary, manually detritylated to deblock the hydroxyl linker arm.

The synthesizer was then programmed to automatically execute the following steps:

1: A "Begin" procedure consisting of a column wash, nucleoside coupling to the support by simultaneous addition (4.0 sec) of nucleoside hemiester (port #7) and coupling reagent (port #8) and a 600 sec wait, column wash, capping of unreacted hydroxyl sites (Cap A + B reagents, 300 sec), column wash, and priming of ports #1, 2, 3, 4, and 9.

2: Synthesis of the 20-base phosphorothioate oligonucleotide sequence dGCCCAAGCTGGCATCCGTCA (Trityl-off).

3: A 15 minute ammonium hydroxide hydrolysis step to cleave the oligonucleotide from the support.

After completion of the ammonium hydroxide hydrolysis, the columns were removed from the synthesizer, manually treated with 0.05 M potassium carbonate/methanol solution (5 min), rinsed with methanol, dried by aspiration

(5 min), re-installed on the synthesizer, and rinsed with anhydrous acetonitrile. The automated synthesis was then repeated (i.e., Steps 1, 2, and 3 above) using the same synthesis column a total of twelve times.

The amount of trityl color released after the first detritylation step was collected and quantitated to determine the amount of nucleoside added to the support - the results are reported in Table 3. The released oligonucleotide solution was deprotected (55°C, 16 h), evaporated to removed ammonia, and quantitated by UV at 260 nm - the results are reported in Table 4. The correct identity of the products, obtained from each of the results shown Table 4, was verified by electrophoresis and comparison to authentic material. Furthermore, no unusual impurities, attributable to the support recycling were present. These results confirmed that each of the nine supports used in this experiment could be reused and in several cases satisfactory results (comparable to new supports) were obtained, even after six or more uses.

Example 5 - SYNTHESIS OF OLIGONUCLEOTIDE PHOSPHOROTHIOATES AND SUPPORT RECYCLING USING METHOXYACETIC ANHYDRIDE CAPPING

This Example illustrates the use of methoxyacetic anhydride as the capping reagent instead of chloroacetic anhydride used in the previous Examples.

The automated DNA synthesizer was set-up with reagents, as described in Example 4, with the exception of the Cap A and B reagents, which were as follows:

Port #10: 0.5 M Methoxyacetic anhydride and 0.5 M 2,6-lutidine in acetonitrile (Cap A).

Port #12: 1 M N-Methylimidazole in acetonitrile (Cap B).

The automated nucleoside derivatization, oligonucleotide synthesis, and support recycling procedure was then performed using the supports listed in

Table 5 and the procedure described in Example 4. However, because of the greater stability of the methoxyacetyl group, the manual column regeneration step with 0.05M potassium carbonate/methanol was increased from 5 min to 15 min.

The amount of trityl color released after the first detritylation step was collected and quantitated to determine the amount of nucleoside added to the support - the results are reported in Table 6. The released oligonucleotide solution was deprotected (55°C, 16 h), evaporated to removed ammonia, and quantitated by UV at 260 nm - the results are reported in Table 7. The composition of the products obtained in Table 7 was examined by gel electrophoresis and the expected products were obtained in each case. This indicated that methoxyacetic anhydride could also be used as a satisfactory capping reagent during the support recycling.

Table 2 - Supports Used For Phosphorothioate Synthesis and Support Recycling

Experiment	Support	Linker Arm	Amount used (mg)
1	Long chain alkylamine CPG	Hydroxyhexylsuccinyldiamide	16.2
2	Long chain alkylamine CPG	Hydroxydodecanoic acid	21.1
3	Glycerol CPG		13.3
4	Toyopearl AF-amino-650M	Hydroxydodecanoic acid	15
5	Aminoethyl polystyrene, Hamilton	Hydroxydodecanoic acid	21.5
6	Aminomethyl polystyrene, Applied Biosystems	Hydroxydodecanoic acid	34.1
7	Pharmacia hydroxyl primer support*	Butanediol diglycidyl	14.5
8	Toyopearl HW65F	Butanediol diglycidyl	15.4
9	Hydroxyethyl polymethacrylate/polystyrene, Hamilton		27.3

*proprietary material supplied by Pharmacia

Table 3 - Nucleoside loading obtained after repetitive synthesis on the same support

	Synthesis # and First Nucleoside Loading Level (µmol/g)											
Experiment	1	2	3	4	5	6	7	8	9	10	11	12
1	74	62	61	65	56	55	54	60	58	60	51	49
2	57	58	54	56	54	54	54	62	51	49	56	46
3	72	68	65	67	64	64	62	61	60	57	55	54
4	96	119	130	130	126	123	65	60	46	34	25	17
5	75	79	76	76	70	57	47	40	43	60	46	40
6	30	35	35	37	38	35	35	36	31	33	37	33
7	155	111	107	97	122	115	95	122	87	110	101	89
8	107	110	116	113	111	104	102	87	76	92	71	66
9	34	41	47	48	48	53	49	50	45	62	51	67

Table 4 - Amount of Crude Oligonucleotide Produced From Repetitive Syntheses on the Same Support

	Synthesis # and amount of crude product produced (A_{260} units)											
Experiment	1	2	3	4	5	6	7	8	9	10	11	12
1	7530	7590	7530	7650	6790	6850	5740	5930	4750	3640	2780	2350
2	7630	7680	6590	6970	6680	6680	6110	5170	3460	2420	2700	1850
3	8350	7740	8270	7970	8120	8120	7440	7370	6690	6170	5190	4660
4	12200	11500	12600	11700	11600	11800	9880	6710	5850	4750	3540	2550
5	8010	8340	7990	7960	7810	6720	5690	3900	3280	3780	2550	2050
6	3610	4300	4220	4540	4830	4560	4630	4620	4300	3730	3390	2750
7	9300	8190	7460	7620	8550	7390	5900	4900	2280	4180	2430	1750
8	11520	11100	10600	11400	11500	11400	9980	n.d.	n.d.	8390	5060	6270
9	2360	3260	4520	4630	5290	6420	6610	n.d.	n.d.	8570	6420	6830

Table 5 - Supports Used For Oligonucleotide Phosphorothioate Synthesis and Support Recycling

Experiment	Support	Linker Arm	Amount used (mg)
1	Glycerol CPG		14.5
2	Toyopearl HW65F	Butanediol diglycidyl	14.6

Table 6 - Nucleoside Loading Obtained After Repetitive Synthesis on the Same Support

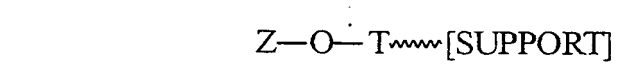
	Synthesis # and first nucleoside loading (μmol/g)											
Experiment	1	2	3	4	5	6	7	8	9	10	11	12
1	83	82	71	75	61	69	63	64	58	56	48	42
2	93	105	115	115	105	114	117	120	110	113	96	67

Table 7 - Amount of Crude Oligonucleotide Produced From Repetitive Syntheses on the Same Support

	Synthesis # and amount of crude product produced (A_{260} units)											
Experiment	1	2	3	4	5	6	7	8	9	10	11	12
1	8100	7750	7570	7850	6910	7500	7440	7400	6870	6810	6210	5220
2	8480	9820	10200	10900	9490	10200	10300	10700	10000	9190	8450	6170

What is claimed is:

1. A reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising the following formula:



wherein Z is a linker moiety and T is an organic radical.

2. The reusable linker arm defined in claim 1, wherein T contains at least one carbon.

3. The reusable linker arm defined in claim 1, wherein T is a C_1-C_{300} organic moiety.

4. The reusable linker arm defined in claim 1, wherein T is a C_1-C_{200} organic moiety.

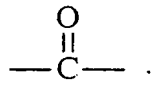
5. The reusable linker arm defined in claim 1, wherein T is a C_1-C_{100} organic moiety.

6. The reusable linker arm defined in claims 1-5, wherein T is a saturated organic moiety.

7. The reusable linker arm defined in claims 1-5, wherein T is an unsaturated organic moiety.

8. The reusable linker arm defined in claim 1, wherein T is a C_1-C_{300} organic moiety comprising at least one heteroatom selected from N and O.

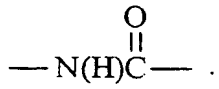
9. The reusable linker arm defined in claims 1-8, wherein the organic moiety comprises at least one moiety having the formula:



10. The reusable linker arm defined in claims 1-8, wherein the organic moiety comprises at least one moiety having the formula:

$$-N(H)-.$$

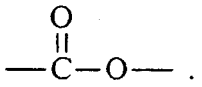
11. The reusable linker arm defined in claims 1-8, wherein the organic moiety comprises at least one moiety having the formula:



12. The reusable linker arm defined in claims 1-8, wherein the organic moiety comprises at least one moiety having the formula:

$$-C-O-C-.$$

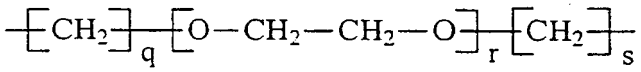
13. The reusable linker arm defined in claims 1-8, wherein organic moiety comprises at least one moiety having the formula:



14. The reusable linker arm defined in claims 1-13, wherein the organic moiety is unsubstituted.

15. The reusable linker arm defined in claim 14, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

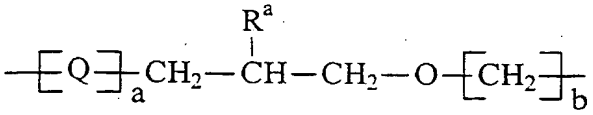
16. The reusable linker arm defined in claims 1-15, wherein T has the formula:



wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

17. The reusable linker arm defined in claim 16, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.

18. The reusable linker arm defined in claims 1-15, wherein T has the formula:



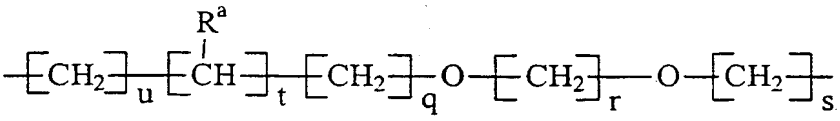
wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, $-NH_2$, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

19. The reusable linker arm defined in claim 18, wherein a is 0 and R^8 is -OH..

20. The reusable linker arm defined in claim 18, wherein a is 1 and R^a is -NR or -OR.

21. The reusable linker arm defined in claims 18-20, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyl-dimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenyl-methoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-methoxypiperidinyl and mixtures thereof.

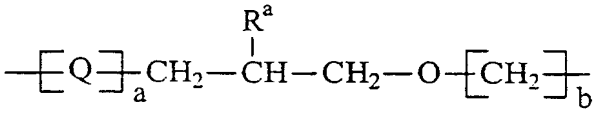
22. The reusable linker arm defined in claim 18, wherein Q comprises a moiety having the formula:



wherein q, r, s, t and u are the same or different and each is an integer having a value of 0-40 and R^a is selected from the group comprising hydrogen, hydroxyl, a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group, a C_5-C_{40} alkylaryl group, $-NH_2$, -NHR and -OR, wherein R is a protecting group.

23. The reusable linker arm defined in claim 22, wherein s is 0, q, r and u are the same or different and each is an integer having a value of 1-10, t is an integer of 1-5 and R^a is hydroxyl.

24. The reusable linker arm defined in claims 1-15, wherein T has the formula:



wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, $-NH_2$, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

25. The reusable linker arm defined in claim 24, wherein a is 0 and R^8 is -OH.

26. The reusable linker arm defined in claim 24, wherein a is 1 and R^a is -NR or -OR.

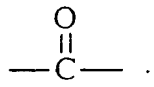
27. The reusable linker arm defined in claim 18, wherein Q is a C_1-C_{100} organic moiety.

28. The reusable linker arm defined in claim 18, wherein Q is a saturated organic moiety.

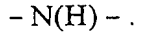
29. The reusable linker arm defined in claim 18, wherein Q is an unsaturated organic moiety.

30. The reusable linker arm defined in claim 18, wherein T is a C_1-C_{100} organic moiety comprising at least one heteroatom selected from N and O.

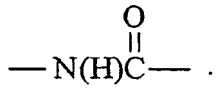
31. The reusable linker arm defined in claims 27-30, wherein the organic moiety comprises at least one moiety having the formula:



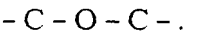
32. The reusable linker arm defined in claims 27-30, wherein the organic moiety comprises at least one moiety having the formula:



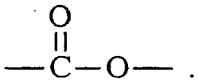
33. The reusable linker arm defined in claims 27-30, wherein the organic moiety comprises at least one moiety having the formula:



34. The reusable linker arm defined in claims 27-30, wherein the organic moiety comprises at least one moiety having the formula:



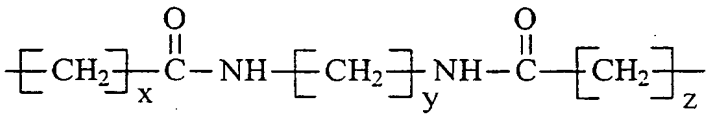
35. The reusable linker arm defined in claims 27-30, wherein organic moiety comprises at least one moiety having the formula:



36. The reusable linker arm defined in claim 27-35, wherein the organic moiety is unsubstituted.

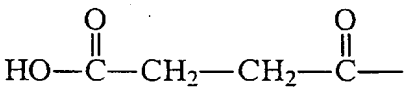
37. The reusable linker arm defined in claim 27-35, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

38. The reusable linker arm defined in claim 18, wherein Q has the formula:

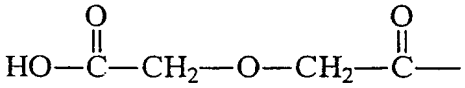


wherein each of x, y and z is an integer having a value of 1-40.

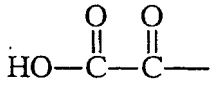
39. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:



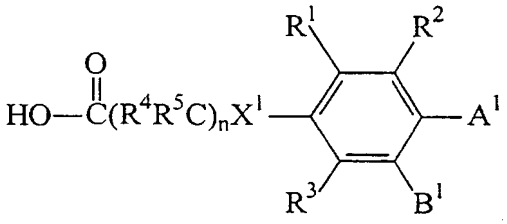
40. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:



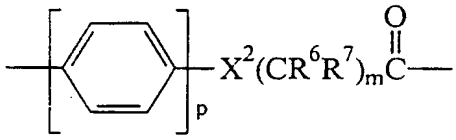
41. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:



42. The reusable linker arm defined in claims 1-38, wherein Z has the following formula:



wherein: R^1, R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:



wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, $-S(O)_2-$ and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, R^6 and R^7 are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and m is 0, 1 or 2.

43. The reusable linker arm defined in claim 42, wherein p is 0.

44. The reusable linker arm defined in claims 42-43, wherein B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group.

45. The reusable linker arm defined in claims 42-44, wherein each of R^4, R^5, R^6 and R^7 is hydrogen.

46. The reusable linker arm defined in claims 42-45, wherein each of m and n are 1.

47. The reusable linker arm defined in claims 42-46, wherein each of R^1, R^2 and R^3 is hydrogen.

48. The reusable linker arm defined in claims 42-47, wherein X^1 and X^2 are both -O-.

49. The reusable linker arm defined in claims 1-48, wherein SUPPORT is an inorganic substance.

50. The reusable linker arm defined in claim 49, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

51. The reusable linker arm defined in claims 1-48, wherein SUPPORT is an organic substance.

52. The reusable linker arm defined in claim 51, wherein the organic substance is a cross-linked polymer.

53. A reusable linker arm for solid support oligonucleotide synthesis, the linker arm comprising the following formula:

NUCLEOSIDE—Z—O—T~~~[SUPPORT]

wherein Z is a linker moiety and T is an organic radical.

54. The reusable linker arm defined in claim 53, wherein T contains at least one carbon.

55. The reusable linker arm defined in claim 53, wherein T is a C_1-C_{300} organic moiety.

56. The reusable linker arm defined in claim 53, wherein T is a C_1-C_{200} organic moiety.

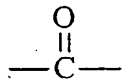
57. The reusable linker arm defined in claim 53, wherein T is a C_1-C_{100} organic moiety.

58. The reusable linker arm defined in claims 53-57, wherein T is a saturated organic moiety.

59. The reusable linker arm defined in claims 53-57, wherein T is an unsaturated organic moiety.

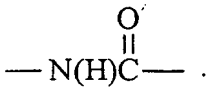
60. The reusable linker arm defined in claims 53-57, wherein T is a C_1-C_{300} organic moiety comprising at least one heteroatom selected from N and O.

61. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:



62. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:

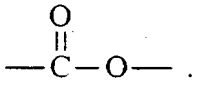
63. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:



64. The reusable linker arm defined in claims 53-60, wherein the organic moiety comprises at least one moiety having the formula:

$$-C-O-C-.$$

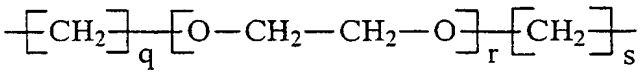
65. The reusable linker arm defined in claims 53-60, wherein organic moiety comprises at least one moiety having the formula:



66. The reusable linker arm defined in claims 53-65, wherein the organic moiety is unsubstituted.

67. The reusable linker arm defined in claims 53-65, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

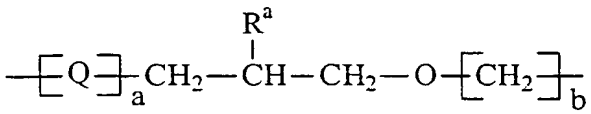
68. The reusable linker arm defined in claims 53-67, wherein T has the formula:



wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

69. The reusable linker arm defined in claim 68, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.

70. The reusable linker arm defined in claims 53-67, wherein T has the formula:



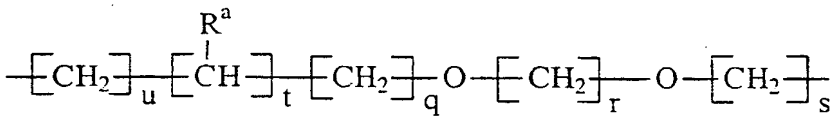
wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, $-NH_2$, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

71. The reusable linker arm defined in claim 70, wherein a is 0 and R^8 is -OH..

72. The reusable linker arm defined in claim 70, wherein a is 1 and R^a is -NR or -OR.

73. The reusable linker arm defined in claims 70-72, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, . trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyldimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenylmethoxycarbonyl, 2-phenylsulfonyl-ethoxycarbony, fluorophenyl-methoxypiperidinyl and mixtures thereof.

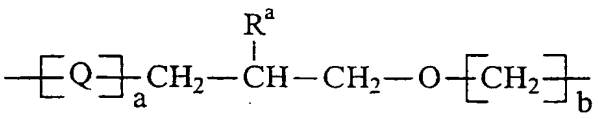
74. The reusable linker arm defined in claim 70, wherein Q comprises a moiety having the formula:



wherein q, r, s, t and u are the same or different and each is an integer having a value of 0-40 and R^a is selected from the group comprising hydrogen, hydroxyl, a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group, a C_5-C_{40} alkylaryl group, $-NH_2$, -NHR and -OR, wherein R is a protecting group.

75. The reusable linker arm defined in claim 74, wherein s is 0, q, r and u are the same or different and each is an integer having a value of 1-10, t is an integer of 1-5 and R^a is hydroxyl.

76. The reusable linker arm defined in claim 70, wherein T has the formula:



wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, $-NH_2$, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

77. The reusable linker arm defined in claim 76, wherein a is 0 and R^8 is -OH.

78. The reusable linker arm defined in claim 76, wherein a is 1 and R^a is -NR or -OR.

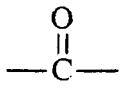
79. The reusable linker arm defined in claims 53-78, wherein Q is a C_1-C_{100} organic moiety.

80. The reusable linker arm defined in claims 53-78, wherein Q is a saturated organic moiety.

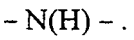
81. The reusable linker arm defined in claims 53-78, wherein Q is an unsaturated organic moiety.

82. The reusable linker arm defined in claims 53-78, wherein T is a C_1-C_{100} organic moiety comprising at least one heteroatom selected from N and O.

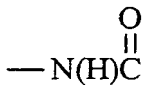
83. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:



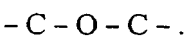
84. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:



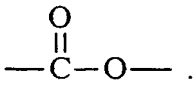
85. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:



86. The reusable linker arm defined in claims 76-82, wherein the organic moiety comprises at least one moiety having the formula:



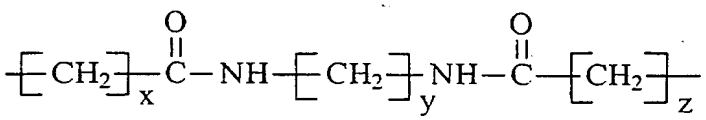
87. The reusable linker arm defined in claims 76-82, wherein organic moiety comprises at least one moiety having the formula:



88. The reusable linker arm defined in claims 76-87, wherein the organic moiety is unsubstituted.

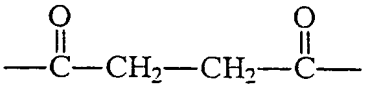
89. The reusable linker arm defined in claims 76-87, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

90. The reusable linker arm defined in claim 53, wherein Q has the formula:

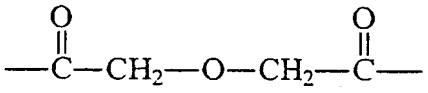


wherein each of x, y and z is an integer having a value of 1-40.

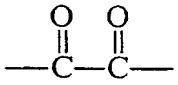
91. The reusable linker arm defined in claims 53-90, wherein Z has the following formula:



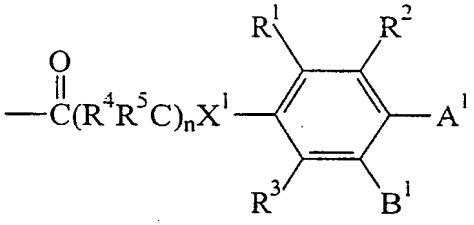
92. The reusable linker arm defined in claims 53-90, wherein Z has the following formula:



93. The reusable linker arm defined in claims 53-90, wherein Z has the following formula:

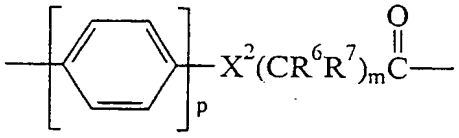


94. The reusable linker arm defined in claims 53-90, wherein Z has the following formula:



wherein: R^1, R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or

unsubstituted C_5-C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:



wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, R^6 and R^7 are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and m is 0, 1 or 2.

95. The reusable linker arm defined in claim 94, wherein p is 0.

96. The reusable linker arm defined in claims 94-95, wherein B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group.

97. The reusable linker arm defined in claims 94-96, wherein each of R^4, R^5, R^6 and R^7 is hydrogen.

98. The reusable linker arm defined in claims 94-97, wherein each of m and n are 1.

99. The reusable linker arm defined in claims 94-98, wherein each of R^1, R^2 and R^3 is hydrogen.

100. The reusable linker arm defined in claims 94-99, wherein X^1 and X^2 are both -O-.

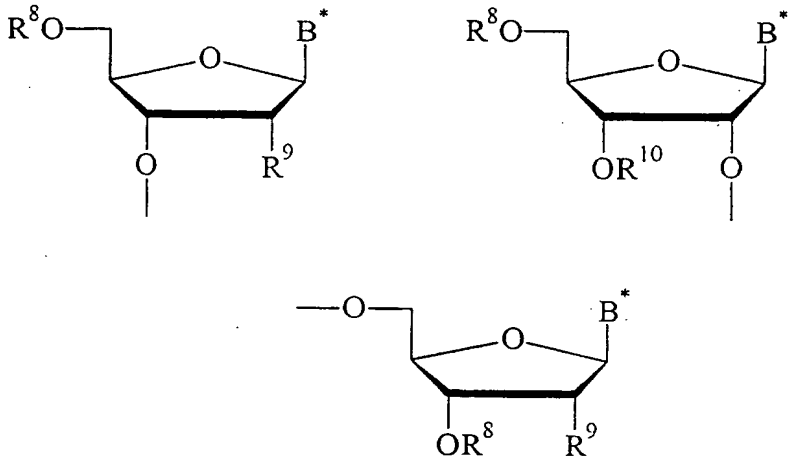
101. The reusable linker arm defined in claims 53-100, wherein SUPPORT is an inorganic substance.

102. The reusable linker arm defined in claim 101, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

103. The reusable linker arm defined in claims 53-100, wherein SUPPORT is an organic substance.

104. The reusable linker arm defined in claim 103, wherein the organic substance is a cross-linked polymer.

105. The reusable linker arm defined in claims 53-104, wherein NUCLEOSIDE is a moiety selected from one of the following formulae:

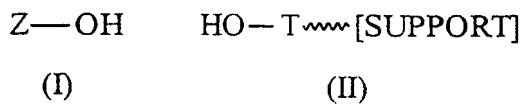


wherein R^8 and R^{10} are the same or different and are hydrogen or a protecting group, R^9 is hydrogen or $-OR^{11}$ wherein R^{11} is hydrogen or a protecting group, and B^* is a nucleic acid base.

106. A process for production of a reusable linker arm for oligonucleotide synthesis having the following formula:

Z—O—T〰[SUPPORT]

wherein Z is a linker moiety and T is an organic radical, the process comprising the step of reacting together the compound of Formulae I and II:



(I) (II)

wherein Z and T are as defined above.

107. The process defined in claim 106, wherein T contains at least one carbon.

108. The process defined in claim 106, wherein T is a C_1-C_{300} organic moiety.

109. The process defined in claim 106, wherein T is a C_1-C_{200} organic moiety.

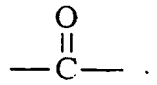
110. The process defined in claim 106, wherein T is a C_1-C_{100} organic moiety.

111. The process defined in claims 106-110, wherein T is a saturated organic moiety.

112. The process defined in claims 106-110, wherein T is an unsaturated organic moiety.

113. The process defined in claims 106-112, wherein T is a C_1-C_{300} organic moiety comprising at least one heteroatom selected from N and O.

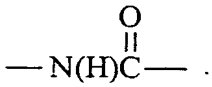
114. The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:



115. The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:

$$-N(H)-.$$

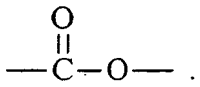
116. The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:



117. The process defined in claims 106-113, wherein the organic moiety comprises at least one moiety having the formula:

$$-C-O-C-.$$

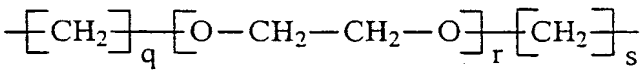
118. The process defined in claims 106-113, wherein organic moiety comprises at least one moiety having the formula:



119. The process defined in claims 106-118, wherein the organic moiety is unsubstituted.

120. The process defined in claims 106-118, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

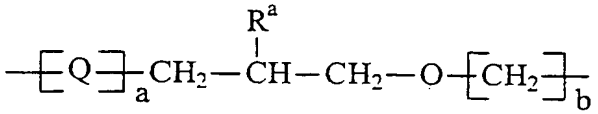
121. The process defined in claims 106-120, wherein T has the formula:



wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

122. The process defined in claim 121, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.

123. The process defined in claims 106-120, wherein T has the formula:



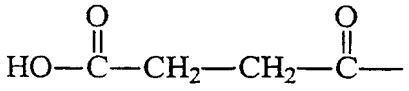
wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, $-NH_2$, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

124. The reusable linker arm defined in claim 123, wherein a is 0 and R^a is -OH..

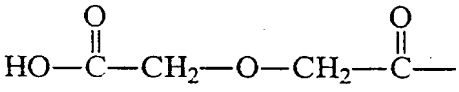
125. The reusable linker arm defined in claim 123, wherein a is 1 and R^a is -NR or -OR.

126. The process defined in claims 123-125, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyl-dimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenyl-methoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-methoxypiperidinyl and mixtures thereof.

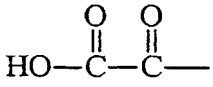
127. The process defined in claims 106-126, wherein Z has the following formula:



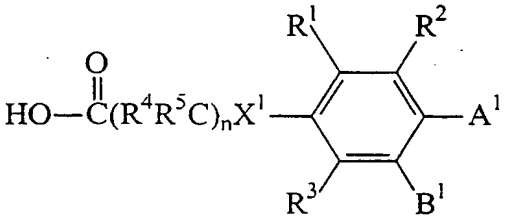
128. The process defined in claims 106-126, wherein Z has the following formula:



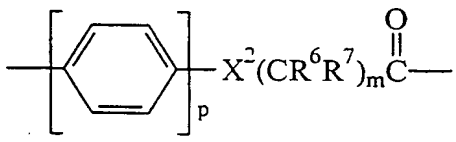
129. The process defined in claims 106-126, wherein Z has the following formula:



130. The process defined in claims 106-126, wherein Z has the following formula:



wherein: R^1, R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:



wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, R^6 and

R^7 are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and m is 0, 1 or 2.

131. The process defined in claim 130, wherein p is 0.

132. The process defined in claims 130-131, wherein B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group.

133. The process defined in claims 130-132, wherein each of R^4, R^5, R^6 and R^7 is hydrogen.

134. The process defined in claims 130-133, wherein each of m and n are 1.

135. The process defined in claims 130-134, wherein each of R^1, R^2 and R^3 is hydrogen.

136. The process defined in claims 130-135, wherein X^1 and X^2 are both -O-.

137. The process defined in claims 106-136, wherein SUPPORT is an inorganic substance.

138. The process defined in claim 137, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

139. The process defined in claims 106-136, wherein SUPPORT is an organic substance.

140. The process defined in claim 139, wherein the organic substance is a cross-linked polymer.

141. The process defined in claims 106-140, wherein the process is conducted in the presence of an activating agent.

142. The process defined in claim 141, wherein the acitivating agent comprises at least one member selected from the group comprising an acid chloride; an active ester (e.g., nitrophenyl, nitrophenylthio, trichlorophenyl, trifluorophenyl, pentachlorophenyl, pentafluorophenyl, or 3-hydroxy-2,3-dihydro-4-oxo-benzotriazine esters); an active hydroxylamine ester (e.g., N-hydroxyphthalimide or N-hydroxysuccinimide); acid anhydride and mixed anhydride.

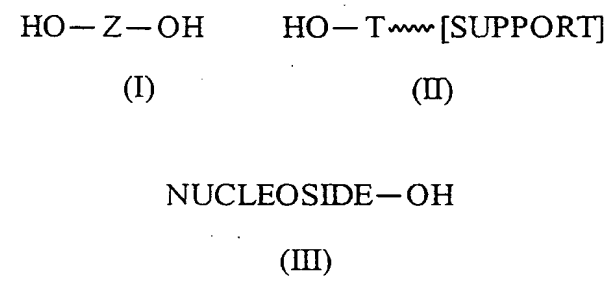
143. The process defined in claim 141, wherein the activating agent comprises at least one member selected from the group comprising arylsulfonyl chlorides (e.g., benzenesulfonyl chloride (BS-Cl), mesitylenesulfonyl chloride (MS-Cl), triisopropylsulfonylchloride (TPS-Cl)); active arylsulfonyl esters (e.g., imidazole, triazole, nitrotriazole, or tetrazole esters of BS-Cl, MS-Cl or TPS-Cl); 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ); acyl carbonates; 1,1'-(carbonyldioxy)dibenzotriazoles; chlorotrimethylsilane; carbodiimides (e.g., dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-ethylcarbodiimide (DEC), diisopropylcarbodiimide (DIC)) either alone or in combination with auxillary nucleophiles (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)); or uronium salts (e.g., tetramethyluronium chloride (TMU-Cl), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDBTU), 2-(2-

oxo-1(2H)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate (HAMDU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (HAMTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate (HApipU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate (HAPyU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)) either alone or in combination with auxillary nucleophiles (i.e., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)) or phosphonium salts (e.g., benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP), 2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate (BOI), bromo tris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP), 7-azabenzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (AOP), and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)) either alone or in combination with auxillary nucleophiles and/or catalysts.

144. A process for production of a reusable linker arm for oligonucleotide synthesis having the following formula:

NUCLEOSIDE—Z—O—T〰[SUPPORT]

wherein Z is a linker moiety and T is an organic radical, the process comprising the step of reacting together the compounds of Formulae I, II and III:



wherein Z and T are as defined above.

145. The process defined in claim 144, wherein T contains at least one carbon.

146. The process defined in claim 144, wherein T is a C_1-C_{300} organic moiety.

147. The process defined in claim 144, wherein T is a C_1-C_{200} organic moiety.

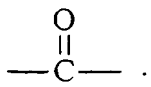
148. The process defined in claim 144, wherein T is a C_1-C_{100} organic moiety.

149. The process defined in claims 144-148, wherein T is a saturated organic moiety.

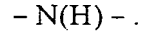
150. The process defined in claims 144-148, wherein T is an unsaturated organic moiety.

151. The process defined in claims 144-148, wherein T is a C_1-C_{300} organic moiety comprising at least one heteroatom selected from N and O.

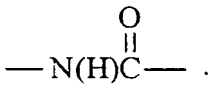
152. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:



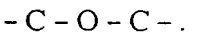
153. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:



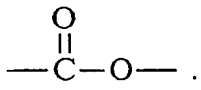
154. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:



155. The process defined in claims 144-151, wherein the organic moiety comprises at least one moiety having the formula:



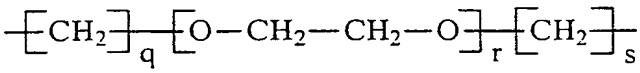
156. The process defined in claims 144-151, wherein organic moiety comprises at least one moiety having the formula:



157. The process defined in claims 144-156, wherein the organic moiety is unsubstituted.

158. The process defined in claims 144-156, wherein the organic moiety is substituted by at least one moiety selected from the group comprising a C_1-C_{40} alkyl group, a C_5-C_{40} aryl group, a C_1-C_{40} alkoxy group, a C_1-C_{40} ester group,a C_1-C_{40} hydroxy group, a C_2-C_{40} acrylate group and a C_5-C_{40} alkylaryl group.

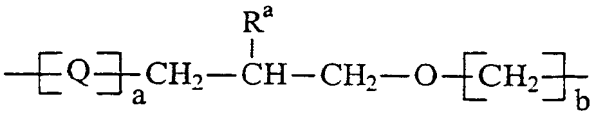
159. The process defined in claims 144-158, wherein T has the formula:



wherein q and s are the same or different and each is an integer having a value of 0-40 and r is an integer having a value of 1-200.

160. The process defined in claim 159, wherein q and s are the same or different and each is an integer having a value of 1-20 and r is an integer having a value of 1-150.

161. The process defined in claim 144-158, wherein T has the formula:



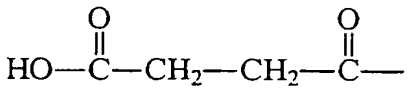
wherein a is 0 or 1, Q is an organic moiety, R^a is selected from -OH, $-NH_2$, -NR and -OR wherein R is a protecting group and b is an integer having a value of 0-40.

162. The reusable linker arm defined in claim 161, wherein a is 0 and R^δ is -OH..

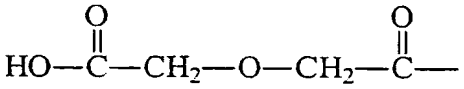
163. The reusable linker arm defined in claim 161, wherein a is 1 and R^a is -NR or -OR.

164. The process defined in claims 161-163, wherein the protecting group is selected from the group comprising acetyl, chloroacetyl, methoxyacetyl, t-butyl phenoxyacetyl, trityl, methoxytrityl, dimethoxytrityl (DMT), dialkylphosphite, pivalyl-isobutyloxycarbonyl, *t*-butyldimethylsilyl, phenoxyacetal, 9-phenylxanthen-9-yl (pixyl), tetrahydropyranyl, methoxytetrahydropyranyl, methoxymethyl, benzyloxymethyl, methoxyethoxymethyl, methylthiomethyl, dialkylphosphate, levulinyl, dimethylphenylsilyl, trimethylsilyl, isopropyl-dimethylsilyl, diisopropylmethylsilyl, diethylisopropylsilyl, triisopropylsilyl, benzoyl, pivaloyl, trifluoroacetyl, allyl, benzyl, o-nitrobenzyl, o-hydroxystyryldimethylsilyl, 2-oxo-1,2-diphenylethyl, allyloxycarbonyl, monomethoxymethyl, nitroveratryloxycarbonyl, dimethoxybenzoin, dimethoxybenzoin carbonate, methylnitropiperonyl carbonate, fluorenyl-methoxycarbonyl, 2-phenylsulfonylethoxycarbony, fluorophenyl-methoxypiperidinyl and mixtures thereof.

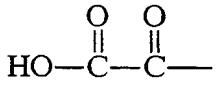
165. The process defined in claims 144-164, wherein Z has the following formula:



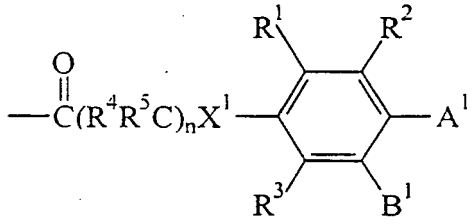
166. The process defined in claims 144-164, wherein Z has the following formula:



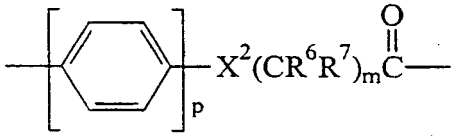
167. The process defined in claims 144-164, wherein Z has the following formula:



168. The process defined in claims 144-164, wherein Z has the following formula:



wherein: R^1, R^2 and R^3 are the same or different and are selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; R^4 and R^5 are the same or different and are selected from the group consisting of hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; X^1 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-; R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group; n is 0, 1 or 2; and one of A^1 and B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and the other of A^1 and B^1 has the formula:



wherein p is 0 or 1, X^2 is selected from the group consisting of -O-, -S-, -C(O)-, -$S(O)_2$- and -N(R)-, R is selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, R^6 and

R^7 are the same or different and are selected from the group comprising hydrogen, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group, and m is 0, 1 or 2.

169. The process defined in claim 168, wherein p is 0.

170. The process defined in claims 168-169, wherein B^1 is selected from the group consisting of hydrogen, halide, a substituted or unsubstituted C_1-C_{20} alkyl group, a substituted or unsubstituted C_5-C_{30} aryl group and a substituted or unsubstituted C_5-C_{40} alkylaryl group.

171. The process defined in claims 168-170, wherein each of R^4, R^5, R^6 and R^7 is hydrogen.

172. The process defined in claims 168-171, wherein each of m and n are 1.

173. The process defined in claims 168-172, wherein each of R^1, R^2 and R^3 is hydrogen.

174. The process defined in claims 168-172, wherein X^1 and X^2 are both -O-.

175. The process defined in claims 144-174, wherein SUPPORT is an inorganic substance.

176. The process defined in claim 175, wherein the inorganic substance is selected from the group consisting of silica, glass beads, porous glass, aluminosilicates, borosilicates, metal oxides, clays and mixtures thereof.

177. The process defined in claims 144-174, wherein SUPPORT is an organic substance.

178. The process defined in claim 177, wherein the organic substance is a cross-linked polymer.

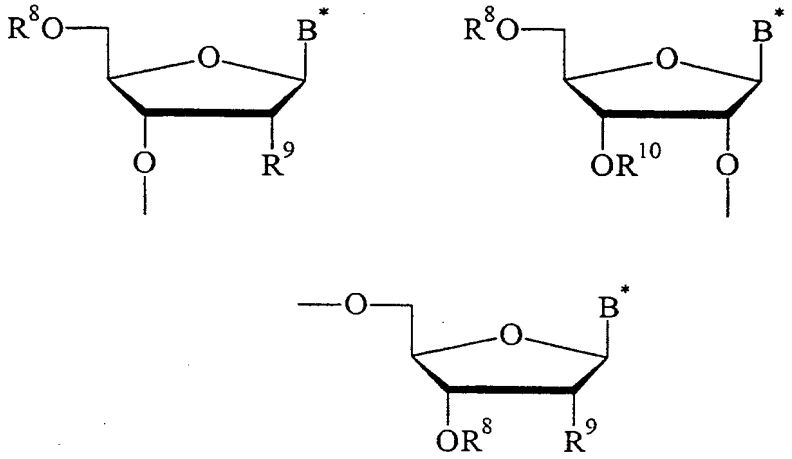
179. The process defined in claims 144-178, wherein the process is conducted in the presence of an activating agent.

180. The process defined in claim 179, wherein the acitivating agent comprises at least one member selected from the group comprising an acid chloride; an active ester (e.g., nitrophenyl, nitrophenylthio, trichlorophenyl, trifluorophenyl, pentachlorophenyl, pentafluorophenyl, or 3-hydroxy-2,3-dihydro-4-oxo-benzotriazine esters); an active hydroxylamine ester (e.g., N-hydroxyphthalimide or N-hydroxysuccinimide); acid anhydride and mixed anhydride.

181. The process defined in claim 179, wherein the activating agent comprises at least one member selected from the group comprising arylsulfonyl chlorides (e.g., benzenesulfonyl chloride (BS-Cl), mesitylenesulfonyl chloride (MS-Cl), triisopropylsulfonylchloride (TPS-Cl)); active arylsulfonyl esters (e.g., imidazole, triazole, nitrotriazole, or tetrazole esters of BS-Cl, MS-Cl or TPS-Cl); 2-ethoxy-1-(ethoxycarbonyl)-1.2-dihydroquinoline (EEDQ); acyl carbonates; 1,1'-(carbonyldioxy)dibenzotriazoles; chlorotrimethylsilane; carbodiimides (e.g., dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-ethylcarbodiimide (DEC), diisopropylcarbodiimide (DIC)) either alone or in combination with auxillary nucleophiles (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)); or uronium salts (e.g., tetramethyluronium chloride (TMU-Cl), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TDBTU), 2-(2-oxo-1(2H)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), 2-(5-

norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate (HAMDU), O-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate (HAMTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate (HAPipU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate (HAPyU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)) either alone or in combination with auxillary nucleophiles (i.e., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), N-hydroxysuccinimide (HOSu), or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (HOObt)) and/or catalysts (e.g., 4-dimethylaminopyridine (DMAP) or N-methylimidazole (NMI)) or phosphonium salts (e.g., benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate (PyBOP), 2-(benzotriazol-1-yl)oxy-1,3-dimethylimidazolidinium hexafluorophosphate (BOI), bromo tris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP), 7-azabenzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (AOP), and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)) either alone or in combination with auxillary nucleophiles and/or catalysts.

182. The process defined in claims 144-181, wherein NUCLEOSIDE is a moiety selected from one of the following formulae:



wherein R^8 and R^{10} are the same or different and are hydrogen or a protecting group, R^9 is hydrogen or $-OR^{11}$ wherein R^{11} is hydrogen or a protecting group, and B^* is a nucleic acid base.

183. The process defined in claims 144-182, wherein the compounds of Formulae I and II are initially reacted to form a conjugate which is reacted with the compound of Formula III.

184. The process defined in claims 144-182, wherein compounds of Formulae I and III are initially reacted to form a conjugate which is reacted with the compound of Formula II.

185. A process for producing an oligonucleotide having a desired sequence comprising the steps of:

(i) reacting a linker arm having the formula:

NUCLEOSIDE—Z—O—T~~[SUPPORT]

wherein Z is a linker moiety and T is an organic radical, with at least one oligonucleoside base until an oligonucleotide having the desired sequence is produce;

(ii) cleaving the oligonucleotide having the desired sequence to produce a free oligonucleotide have the desired sequence; and a used linker arm; and

(iii) recycling the used linker arm to Step (i).

186. The process defined in claim 185, wherein the used linker arm produced in Step (ii) has the formula:

Z—O—T~~[SUPPORT]

wherein Z is a linker moiety and T is an organic radical.

187. The process defined in claims 185-186, wherein Step (iii) comprises the step of converting the used linker arm to a linker arm having the formula:

NUCLEOSIDE—Z—O—T~~[SUPPORT]

wherein Z is a linker moiety and T is an organic radical.

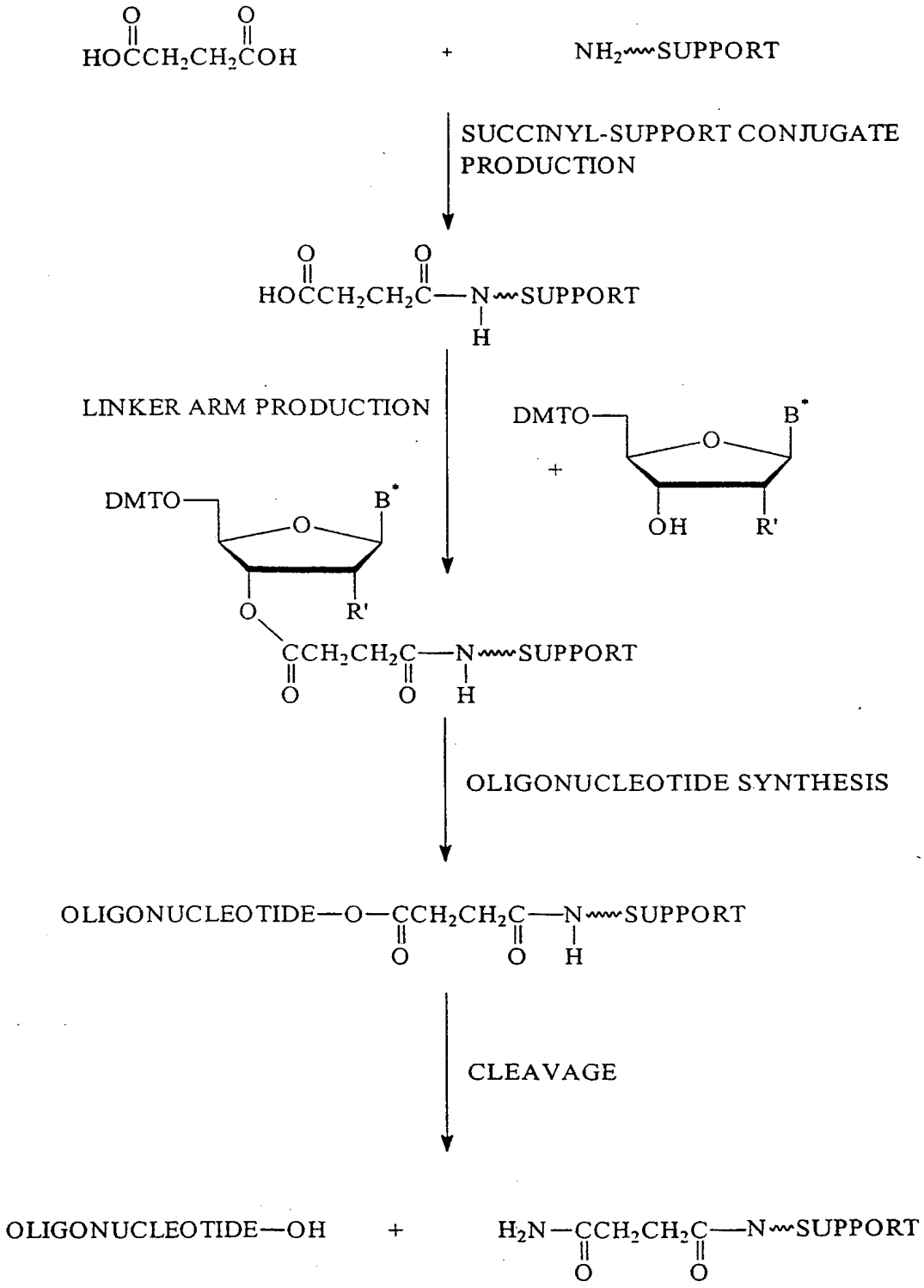


FIGURE 1
(PRIOR ART)

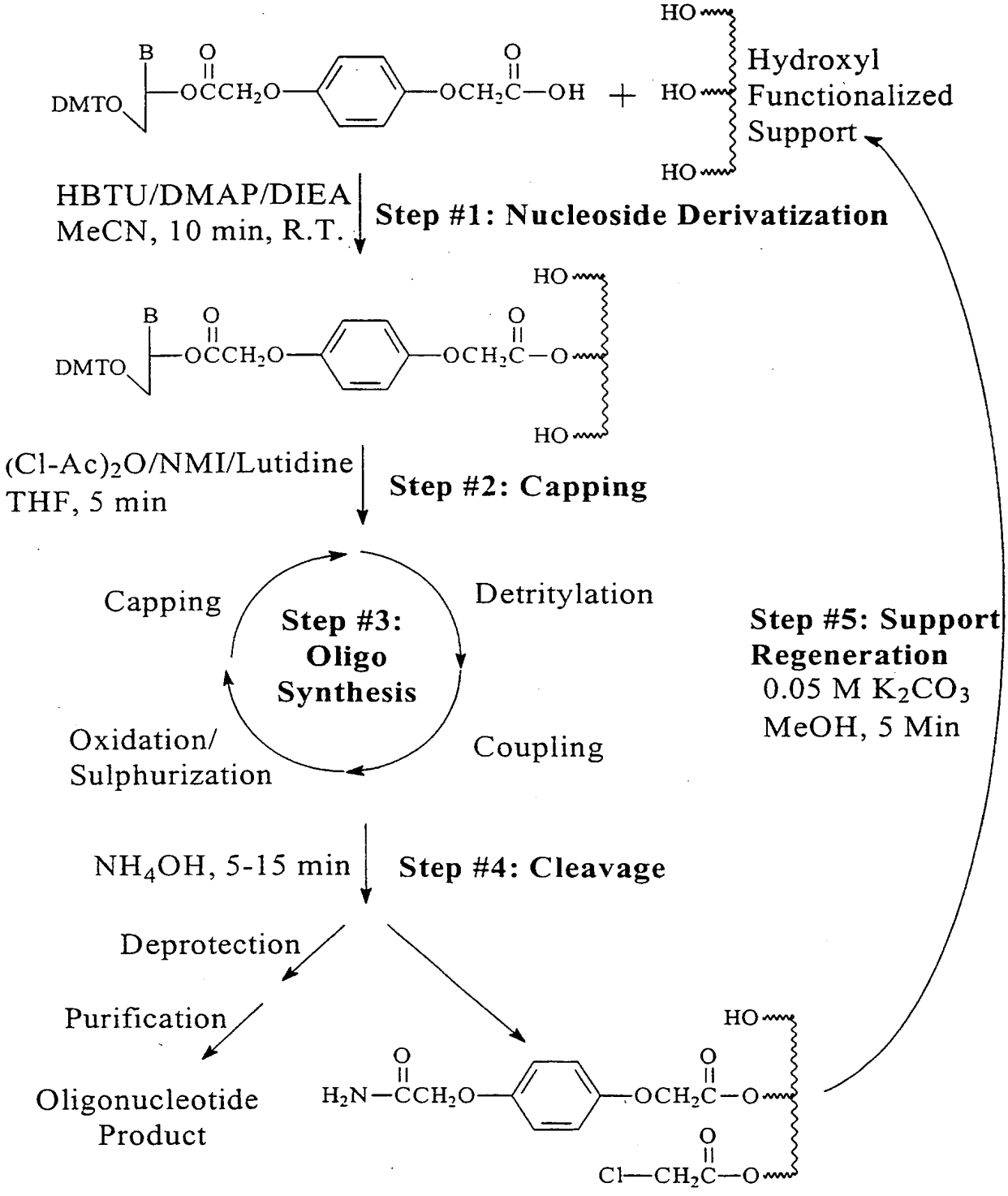
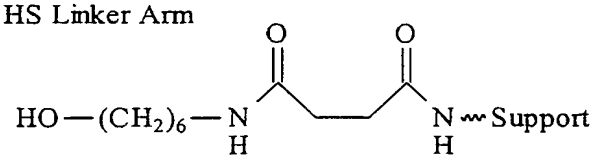
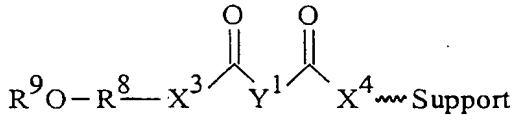

Hydroxyl Functionalized Support
HBTU/DMAP/DIEA
MeCN, 10 min, R.T.
Step #1: Nucleoside Derivatization
(Cl-Ac)2O/NMI/Lutidine
THF, 5 min
Step #2: Capping
Capping
Detritylation
Step #3: Oligo Synthesis
Oxidation/ Sulphurization
Coupling
Step #5: Support Regeneration
0.05 M K2CO3
MeOH, 5 Min
NH4OH, 5-15 min
Step #4: Cleavage
Deprotection
Purification
Oligonucleotide Product

FIGURE 2

A, OHS Linker Arm

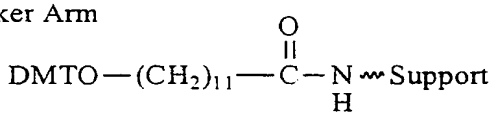


(Preferred example)

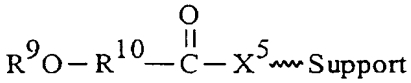


(General example, R^9 = H or protecting group, X^3 and X^4 = NH, NR, or O)

B, C_{12} Linker Arm

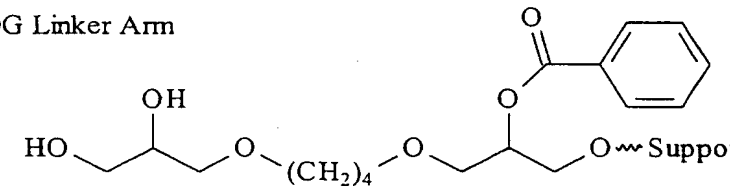


(Preferred example)

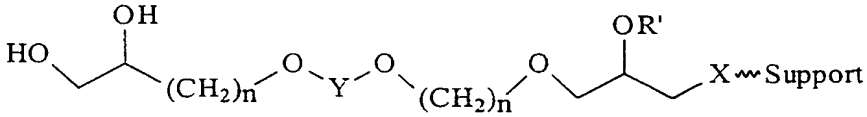


(General example, X^5 = NH, NR,or O)

C, BDG Linker Arm

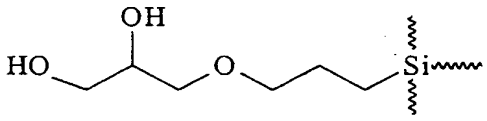


(Preferred example)

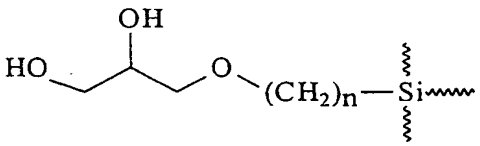


(General example, X = O, NH, or NR, R' = protecting group)

D, GLY Linker Arm (Gly-CPG)



(Preferred example)



(General example)

FIGURE 3

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
PC./CA 99/00600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PON R T ET AL: "Hydroquinone-O,O@?-Diacetic Acid As A More Labile Replacement For Succinic Acid Linkers in Solid-Phase Oligonucleotide Synthesis" TETRAHEDRON LETTERS, vol. 38, no. 19, 12 May 1997 (1997-05-12), page 3327-3330 XP004061417 ISSN: 0040-4039	1-187
X	the whole document, but especially the CPG derivatised nucleotide of scheme 2	1-6, 8-12,15, 42, 45-50, 53-58, 60-66, 94, 97-102, 105, 185-187

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1999	17/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scott, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate. of the relevant passages	Relevant to claim No.

Y	WO 97 23496 A (UNIV TECHNOLOGIES INT ;PON RICHARD T (CA); YU SHUYUAN (CA)) 3 July 1997 (1997-07-03)	1-187
X	the whole document	1-14,42, 45-66, 94, 97-105, 185-187

Y	WO 97 23497 A (UNIV TECHNOLOGIES INT ;PON RICHARD T (CA); YU SHUYUAN (CA)) 3 July 1997 (1997-07-03)	1-187
X	the whole document	1-6, 8-12,15, 42, 45-50, 53-58, 60-66, 94, 97-102, 105, 185-187

Y	US 5 624 711 A (SUNDBERG STEVEN A ET AL) 29 April 1997 (1997-04-29) the whole document	1-187

Y	PON R T ET AL: "Rapid Automated Derivatization of Solid-Phase Supports For Oligonucleotide Synthesis Using Uronium or Phosphonium Coupling Reagents" TETRAHEDRON LETTERS, vol. 38, no. 19, 12 May 1997 (1997-05-12), page 3331-3334 XP004061418 ISSN: 0040-4039 the whole document	1-187

Y	WO 92 06103 A (ICI PLC) 16 April 1992 (1992-04-16) the whole document	1-187

Y	WO 93 07883 A (ISIS PHARMACEUTICALS INC) 29 April 1993 (1993-04-29) the whole document	1-187

	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropnate. of the relevant passages	Relevant to claim No.
T	JAMES I W: "Linkers for Solid Phase Organic Synthesis" TETRAHEDRON, vol. 55, no. 16, 16 April 1999 (1999-04-16), page 4855-4946 XP004161079 ISSN: 0040-4020 page 4859, compound a; page 4865, compound 4; the whole document	1-187

INTERNATIONAL SEARCH REPORT

...ion on patent family members

...ional Application No
...CA 99/00600

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9723496	A	03-07-1997	AU	1027797 A	17-07-1997
			AU	1027897 A	17-07-1997
			CA	2241222 A	03-07-1997
			CA	2241331 A	03-07-1997
			WO	9723497 A	03-07-1997
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